1. NAME OF THE MEDICINAL PRODUCT

Doxorubicin hydrochloride 2 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 2 mg doxorubicin hydrochloride.

Each 5 ml vial contains a total content of doxorubicin hydrochloride of 10 mg.
Each 10 ml vial contains a total content of doxorubicin hydrochloride of 20 mg.
Each 25 ml vial contains a total content of doxorubicin hydrochloride of 50 mg.
Each 75 ml vial contains a total content of doxorubicin hydrochloride of 150 mg.
Each 100 ml vial contains a total content of doxorubicin hydrochloride of 200 mg.

Excipient(s) with known effect:
The product contains sodium chloride (3.5 mg sodium per 1 ml). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

The product is a clear, red solution which is practically free of particles.

4.1 Therapeutic indications

Doxorubicin is a cytotoxic medicinal product that is indicated in the following neoplastic conditions:
- Small-cell lung cancer (SCLC)
- Breast cancer
- Recurrent ovarian carcinoma
- Systemic treatment of local advanced or metastasized bladder carcinoma
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection
- Neoadjuvant and adjuvant therapy of osteosarcoma
- Advanced soft-tissue sarcoma in adults
- Ewing's sarcoma
- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Acute lymphatic leukaemia
- Acute myeloblastic leukaemia
- Advanced multiple myeloma
- Advanced or recurrent endometrial carcinoma
- Wilms' tumour
- Advanced papillary/follicular thyroid cancer
- Anaplastic thyroid cancer
- Advanced neuroblastoma

Doxorubicin is frequently used in combination chemotherapy regimens with other cytostatic medicinal products.

4.2 Posology and method of administration

Treatment with Doxorubicin should be started by or after consultation with a doctor with extensive experience from cytostatic treatment.

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

Doxorubicin must not be used orally, subcutaneously, intramuscularly or intrathecally.

Note: The dosages of S-liposomal doxorubicin and (conventional) doxorubicin are different. The two formulations cannot be interchanged.

Posology

For intravenous use
The dosage of doxorubicin depends on dosage regimen, general status and previous treatment of the patient.

In order to avoid cardiomyopathy, it is recommended that the cumulative total lifetime dose of doxorubicin (including related medicinal products such as daunorubicin) should not exceed 450 - 550 mg/m² body surface area. If patients with concomitant heart disease receive mediastinal and/or heart irradiation, prior treatment with alkylating agents or concomitant treatment with potentially cardiotoxic agents, and high-risk patients (with arterial hypertension since > 5 years, with prior coronary, valvular or myocardial heart damage, age over 70 years) a maximum total dose of 400 mg/m² body surface area should not be exceeded and the cardiac function of these patients should be monitored (see section 4.4).

Dosage is usually calculated on the basis of body surface area. On this basis, a dose of 60 - 75 mg/m² body surface area is recommended every three weeks when doxorubicin is used alone. If it is used in combination with other antitumour agents the dosage of doxorubicin should be reduced to 30 - 40 mg/m² every three weeks.

In patients, who cannot receive the full dose (e.g. in case of immunosuppression, old age), an alternative dosage is 15 - 20 mg/m² body surface area per week.

Patients with prior radiotherapy
Patients who have received prior radiotherapy to the mediastinal/pericardial area should not receive doxorubicin greater than a total cumulative dose of 400 mg/m².

Elderly patients
Dosage may need to be reduced in the elderly.

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/m², whereas in adolescents (over 12 years of age) the maximal cumulative dose is set to 450 mg/m². 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 toxicity. Myelotoxicity should be anticipated, with nadirs at 10 to 14 days after start of treatment.

Hepatic impairment
If hepatic function is impaired, the dosage should be reduced according to the following table:

Serum Bilirubin Levels	BSP Retention	Recommended Dose
20 - 50 µmol/l	9 - 15 %	50 % normal dose
50 -85 µmol/l	Over 15 %	25 % normal dose

Doxorubicin is contraindicated in patients with severe hepatic impairment (>85 µmol/l) (see section 4.3).

Renal impairment
In cases of renal insufficiency with a GFR less than 10 ml/min, 75 % of the calculated dose should be administered.

Obese patients
A reduced starting dose or prolonged dose interval might need to be considered in obese patients (see section 4.4).

For intravesical use
Doxorubicin 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.

Method of administration

Intravenous administration
The solution is given via the tubing of a freely running intravenous infusion of sodium chloride 0.9 % or dextrose 5 % into a large vein using a Butterfly needle, taking 2 to 3 minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation, which can lead to severe local cellulitis and necrosis.

Intravesical administration
The solution should remain in the bladder for 1 - 2 hours. During this period the patient should be turned 90° every 15 minutes. To avoid undesired dilution with urine the patient should be informed not to drink anything for a period of 12 hours before the instillation (this should reduce the production of urine to about 50 ml/h). The instillation may be repeated with an interval of 1 week to 1 month, dependent on whether the treatment is therapeutic or prophylactic.

4.3 Contraindications

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

Contraindications for intravenous administration:
- persistent myelosuppression or severe stomatitis which appeared during previous cytotoxic treatment and/or radiation
- general infection
- severe impaired liver function
- severe arrhythmia, heart failure, previous cardiac infarct, acute inflammatory heart disease
- previous treatment with anthracyclines with maximum cumulative doses (see section 4.4)
- increased haemorrhagic tendency
- breast-feeding

Contraindications of intravesical administration:

- invasive tumours that have penetrated the bladder (beyond T1)
- urinary tract infections
- inflammation of the bladder
- problems with catheterization e.g. urethral stenosis
- haematuria
- breast-feeding

Dosage should not be repeated in the presence or development of bone marrow depression or buccal ulceration. The latter may be preceded by premonitory buccal burning sensations and repetition in the presence of this symptom is not advised.

4.4 Special warnings and precautions for use

Like all chemotherapy, therapy with Doxorubicin hydrochloride should be carried out only under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

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

Before or during treatment with doxorubicin the following monitoring examinations are recommended (how often these examinations are done will depend on the general condition, the dose and the concomitant medication):

- radiographs of the lungs and chest and ECG
- regular monitoring of heart function (LVEF by e.g. ECG, UCG and MUGA scan)
- daily inspection of the oral cavity and pharynx for mucosal changes
- blood tests: haematocrit, platelets, differential white cell count, AST, ALT, LDH, bilirubin, uric acid.

Cardiac toxicity
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 symptoms generally indicate acute transient toxicity. Flattening and widening of the QRS-complex beyond normal limits may indicate doxorubicin hydrochloride-induced cardiomyopathy. As a rule, in patients with a normal LVEF baseline value (= 50 %), a 10 % decrease of absolute value or dropping below the 50 % threshold indicates cardiac dysfunction and in such situation treatment with doxorubicin hydrochloride should be carefully considered.

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 left ventricular ejection fraction (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

medicinal product.

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/m² slowly increases up to the total cumulative dose of 450 - 550 mg/m². Thereafter, the risk of developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m². If the patient has other potential risk factors of cardiotoxicity (history of cardiovascular disease, previous therapy with other anthracyclines or anthracenediones, prior or concomitant radiotherapy to the mediastinal/pericardial area, and concomitant use of medicinal products with the ability to suppress cardiac contractility, including cyclophosphamide and 5-fluoruracil), cardiotoxicity with doxorubicin may occur at lower cumulative doses and cardiac function should be carefully monitored.

Children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration. There may be a greater risk for females than males for cardiotoxicity. Follow-up cardiac evaluations are recommended periodically to monitor the effect.
It is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive. Pre-treatment with digoxin (250 µg daily starting 7 days before doxorubicin) showed a protective effect against cardiotoxicity.

Myelosuppression
There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematological monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10 - 14 days after treatment, with recovery usually occurring by the 21st day. White blood cell counts as low as 1,000/mm³ are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored, since they may also be depressed. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone infiltration by tumour, impaired liver function (when appropriate dosage reduction has not been adopted) and simultaneous treatment with other myelosuppressive agents. Haematological toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or haemorrhage. Careful haematological monitoring is required due to the myelosuppressive effects.

The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA damaging antineoplastic agents. Such cases could have a short (1 - 3 year) latency period.

Radiotherapy
Special caution is mandatory for patients who have had radiotherapy previously, are having radiotherapy concurrently or are planning to have radiotherapy. These patients are at special risk of local reactions in the radiation field (recall phenomenon) if doxorubicin is used. Severe, sometimes fatal, hepatotoxicity (liver damage) has been reported in this connection. Prior radiation to the mediastinum increases the cardiotoxicity of doxorubicin. The cumulative dose of 400 mg/m² must not

be exceeded especially in this case.

Immunosuppression
Doxorubicin is a powerful but temporary immunosuppressant agent. Appropriate measures should be taken to prevent secondary infection.

Vaccines
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. Contact to persons recently vaccinated against polio should be avoided.

Enhanced toxicity
It has been reported that doxorubicin may enhance the severity of the toxicity of other anticancer therapies, such as cyclophosphamide induced haemorrhagic cystitis, mucositis induced by radiotherapy, hepatotoxicity of 6-mercaptopurine and the toxicity of streptozocin or methotrexate (see section 4.5).

Hepatic impairment
Toxicity to recommended doses of doxorubicin is enhanced by hepatic impairment. It is recommended that an evaluation of hepatic function be carried out prior to individual dosing, using conventional clinical laboratory tests such as AST, ALT, alkaline phosphatase, bilirubin and BSP. If required, dosage schedules should be reduced accordingly (see section 4.2).

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

In women, doxorubicin may cause amenorrhoea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy.

Administration site conditions
Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration.
On intravenous administration of doxorubicin, a stinging or burning sensation signifies extravasation. Even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein. 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.

Doxorubicin must not be given intrathecally or intramuscularly or by long-term infusion. Direct intravenous infusion is not advised due to the tissue damage that may occur if the infusion infiltrates

the tissues. If a central vein catheter is used then infusion of doxorubicin in sodium chloride 0.9 % injection is advised.

Others
Precaution is also required during simultaneous or previous radiotherapy of the mediastinal/pericardial area or after treatment with other cardiotoxic substances.

Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies rapid lysis of neoplastic cells induced by the medicinal product (tumour-lysis syndrome) (see section 4.8). 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.

Sodium

This medicinal product contains 0.154 mmol (or 3.54 mg) sodium per ml of solution for infusion, which needs to be taken into consideration by patients on a controlled sodium diet. The different pack sizes of this medicinal product contain the following amounts of sodium:

5 ml vial:	This pack size contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.
10 ml vial:	This pack size contains 35.42 mg sodium, equivalent to 1.77% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
25 ml vial:	This pack size contains 88.55 mg sodium, equivalent to 4.43% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
75 ml vial:	This pack size contains 265.65 mg sodium, equivalent to 13.28% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
100 ml vial:	This pack size contains 354.20 mg sodium, equivalent to 17.71% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Intravesical administration
Intravesical administration of doxorubicin may cause symptoms of chemical cystitis (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall).
Special attention is needed in case of catheter problems (i.e. urethral obstruction caused by invasion of intravesical tumour).
Intravesical administration is contraindicated for tumours that have penetrated the bladder (beyond T1).
The intravesical route of administration should not be attempted in patients with invasive tumours that have penetrated the bladder wall, urinary tract infections, inflammatory conditions of the bladder.

The patient should be informed that the urine might be reddish, particularly in the first specimen after administration, but that this is no cause for alarm.

This medicinal product contains 3.5 mg sodium per 1 ml of doxorubicin hydrochloride solution for infusion. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of other antineoplastic agents, e.g.: anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, dactinomycin, fluorouracil, mitomycin C and taxanes can potentiate the risk of doxorubicin-induced congestive heart failure. The disposition of doxorubicin was found to be significantly altered when it was administered immediately after a short intravenous infusion of paclitaxel. The co-administration of paclitaxel causes a decreased clearance of doxorubicin and more neutropenic and stomatitis episodes have been observed.

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 in combination for the time being, except in well controlled clinical studies where the cardiac function is monitored. See section 4.4 for more details.

Concurrent treatment with 400 mg sorafenib 2 x daily revealed cases with an increase in the AUC of doxorubicin by 21%-47% as well as cases without changes in AUC. The clinical relevance of these results is not known.

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 in connection with combination therapies with cytarabine have been reported.

If doxorubicin therapy is followed by administration of cyclophosphamide, an increased rate of haemorrhagic cystitis has been reported.

As doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. mercaptopurine, methotrexate, streptozocin) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the medicinal product. Dosing of doxorubicin must be modified if concomitant therapy with hepatotoxic medicinal products is mandatory.

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 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 an increase in the concentration and clinical effects and/or toxicity of doxorubicin. Conversely, concomitant administration of inducers of CYP450, such as rifampicin and barbiturates, might decrease plasma concentrations of doxorubicin and reduce efficacy.

Cyclosporine, an inhibitor of CYP3A4 and P-gp, increased the AUC of doxorubicin and doxorubicinol by 55 % and 350 %, respectively. The combination might require dose adjustment. Literature reports suggest that the addition of cyclosporine to doxorubicin results in more severe and prolonged haematological toxicity than with doxorubicin alone. Coma and seizures have also been reported with concomitant administration of cyclosporine and doxorubicin.

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

Disturbed haemotopoesis has been observed after co-administration of substances influencing the bone-marrow function (e.g. amidopyrine derivatives, antiretroviral medicinal products, chloramphenicol, phenytoin, sulphonamides). Increased neutropenia and thrombocytopenia have been reported after simultaneous use of progesterone. Marked nephrotoxicity of Amphotericin B can occur during doxorubicin therapy. Elevated serum doxorubicin concentrations were reported after the concomitant administration of doxorubicin and ritonavir.

Increased cardiotoxicity has also been reported after simultaneous intake of cardioactive medicinal products, e.g., calcium channel blockers and verapamil (with an increase of doxorubicin peak levels, terminal half-life and volume of distribution). The bioavailability of digoxin decreases during doxorubicin therapy. Careful monitoring of the heart function is required in all such concomitant therapeutic regimens.

The absorption of antiepileptic medicinal products (e.g. carbamazepine, phenytoin, valproate) is

decreased after concomitant use of doxorubicin.

Clozapine may increase the risk and severity of the hematologic toxicity of Doxorubicin.

Doxorubicin may reduce oral bioavailability of digoxin.

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

Live vaccines must not be used during doxorubicin therapy due to the risk of generalised disease, which may be lethal. The risk is increased in patients who are immunodepressed due to the underlying disease. During treatment with doxorubicin patients should also avoid contact with recently polio vaccinated persons.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Doxorubicin should not be given during pregnancy. In general, cytostatics should only be administered during pregnancy on strict indication, and the benefit to the mother weighed against possible hazards to the foetus. In animal studies, doxorubicin has shown embryo-, feto- and teratogenic effects (see section 5.3).

In case of the wish to have children after completion of therapy with doxorubicin, patients are advised to consult a genetic counselling centre first.

Contraception in males and females
Woman of childbearing potential should be advised to avoid becoming pregnant and to use effective contraception during treatment and for at least 7 months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with doxorubicin and for at least 4 months after the last dose (see section 4.4).

Breast-feeding
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 and for at least 2 weeks after the last dose (see section 4.3).

Fertility
In women, doxorubicin may cause infertility during the period of administration of the medicinal product. Men being treated with doxorubicin are advised to seek advice on cryo-conservation (or cryo-preservation) of sperm prior to treatment because of the possibility of potentially irreversible infertility due to therapy with doxorubicin. In animal studies, a toxic effect of doxorubicin on the male reproductive organs (testicular atrophy, diffuse degeneration of the spermatic ducts and hypospermia) has been observed.

4.7 Effects on ability to drive and use machines

Due to the frequent occurrence of nausea and vomiting, driving and operation of machinery should be discouraged.

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, haemorrhages, tissue hypoxia or death. Nausea and vomiting as well as alopecia are seen in almost all patients.

Within each system organ class, the adverse events have been ranked under the headings of frequency, most frequent reactions first. For the evaluation of adverse effects the following frequency specification will be used:

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: Common: Uncommon:	Infection Sepsis, septicaemia Septic shock
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Uncommon:	Secondary acute myeloid leukaemia when given in combination with anti-neoplastic medicinal products which damage the DNA (see section 4.4), acute lymphocytic leukaemia
Blood and lymphatic system disorders	Very common:	Myelosuppression, leukopenia (see section 4.4), neutropenia, anaemia, thrombocytopenia, febrile neutropenia, tissue hypoxia or death as consequence of severe myelosuppression
Immune system disorders	Rare:	Anaphylactic reactions
Metabolism and nutrition disorders	Common: Uncommon: Rare: Very rare:	Anorexia Dehydration Tumour lysis syndrome Hyperuricaemia
Eye disorders	Common: Rare: Not known:	Conjunctivitis Lacrimation Keratitis
Cardiac disorders	Common: Very rare: Not known:	Cardiotoxicity, i.e. cardiomyopathy (2 %; e.g. decrease of LVEF, dyspnoea); sinus tachycardia, congestive heart failure; tachyarrhythmia, ventricular tachycardia, bradycardia, bundle branch block Atrioventricular block Arrhythmia, severe cardiac failure may occur suddenly, without premonitory ECG changes
Vascular disorders	Very common: Common: Uncommon: Very rare: Not known:	Thrombophlebitis Phlebitis, haemorrhage Thromboembolism, phlebosclerosis Shock Hot flushes

Respiratory, thoracic and mediastinal disorders	Rare: Not known:	Respiratory disorders, swelling of the nasal mucosa, tachypnoea and dyspnoea, radiation pneumonitis Bronchospasm
Gastrointestinal disorders	Very common: Common: Uncommon: Very rare:	Nausea/vomiting, mucositis, stomatitis, diarrhoea Oesophagitis, abdominal pain or burning sensation Gastrointestinal haemorrhage, colitis, erosive gastritis, necrotising colitis with sometimes serious infections when doxorubicin and cytarabine are combined, ulceration and necrosis of the colon Erosions, mucosal discoloration
Hepatobiliary disorders	Not known:	Hepatotoxicity
Skin and subcutaneous tissue disorders	Very common: Common: Rare:	Local toxicity, onycholysis, erythema, photosensitivity, palmar–plantar erythrodysaesthesia syndrome, alopecia, rash Pruritus, recall of skin reaction due to prior radiotherapy, skin hyperpigmentation, hyperpigmentation of nail beds, urticaria Tissue necrosis, local erythematous reactions along the vein which was used for the injection
Musculoskeletal and connective tissue disorders	Very rare: Not known:	Generalised muscle weakness Joint pain
Renal and urinary disorders	Common: Not known:	Haemorrhagic cystitis, Local reactions (chemical cystitis) might occur at intravesical treatment (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall and bladder spasms) Red colouration of the urine 1-2 days after administration, acute renal failure, renal damage
Reproductive system and breast disorders	Very rare: Not known:	Amenorrhoea, oligospermia, azoospermia (see section 4.4) Infertility
General disorders and administration site conditions	Very common: Rare: Very rare: Not known:	Fever, asthenia, shivering Dizziness General malaise A stinging or burning sensation at the administration site (see section 4.4)
Investigations	Very common:	Asymptomatic decrease in LVEF, abnormal ECG, abnormal transaminase levels, weight gain[a]
Surgical and medical procedures	Not known:	Extravasation can lead to severe cellulitis, vesication and local tissue necrosis which may require surgical measures (including skin grafts)

[a]In patients with early breast cancer who received adjuvant therapy with doxorubicin

(NSABP B-15 study).
The described side effects of doxorubicin therapy are mostly reversible.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The symptoms of overdosage are likely to be an extension of doxorubicin's pharmacological action. Single doses of 250 mg and 500 mg of doxorubicin have proven to be fatal. Such doses may cause acute myocardial degeneration, cardiac insufficiency including stenocardia, angina pectoris and myocardial infarction within 24 hours, and severe myelosuppression (leukopenia and thrombocytopenia in particular), the greatest effects of which are seen between 10 and 15 days after administration and gastrointestinal toxicity (mainly mucositis). Treatment should aim to support the patient during this period. Particular attention should be given to prevention and treatment of possible severe haemorrhage or infections secondary to severe, persistent bone marrow depression. Blood transfusion, antibiotics and reverse barrier nursing may be considered. Hemoperfusion immediately after the overdose proved to be a rescue measure, too. Delayed cardiac failure may occur up to six months after the overdose. Patients should be observed carefully and, should signs of cardiac failure arise, be treated along conventional lines.

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 conventionally

Doxorubicin cannot be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances)
ATC code: L01DB01

Mechanism of action
Doxorubicin is an anthracycline antibiotic. It exerts its antineoplastic effect via cytotoxic mechanisms of action, especially intercalation into DNA, inhibition of the enzyme topoisomerase II, and formation of reactive oxygen species (ROS). All of these have a deleterious effect on DNA synthesis: Intercalation of the doxorubicin molecule leads to an inhibition of RNA and DNA polymerases by way of disturbances in base recognition and sequence specificity. The inhibition of topoisomerase II produces single and double strand breaks of the DNA helix. Scission of DNA also originates from the chemical reaction with highly reactive oxygen species like the hydroxyl radical $OH^{\bullet}$. Mutagenesis and chromosomal aberrations are the consequences.

The specificity of doxorubicin toxicity appears to be related primarily to proliferative activity

of normal tissue. Thus, bone marrow, gastro-intestinal tract and gonads are the main normal tissues damaged.

An important cause of treatment failure with doxorubicin and other anthracyclines is the development of resistance. In an attempt to overcome cellular resistance to doxorubicin, the use of calcium antagonists such as verapamil has been considered since the primary target is the cell membrane. Verapamil inhibits the slow channel of calcium transport and can enhance cellular uptake of doxorubicin. A combination of doxorubicin and verapamil is associated with severe toxic effects in animal experiments.

5.2 Pharmacokinetic properties

Distribution
Following intravenous injection, doxorubicin is rapidly cleared from the blood, and distributed into tissues including lungs, liver, heart, spleen, lymph nodes, bone marrow and kidneys. Relatively low but persistent levels are found in tumour tissue. It does not cross the blood-brain barrier, but does cross the placenta and is distributed into breast milk. The volume of distribution V_d is 25 l; the degree of protein binding is 60 – 70 %.

Biotransformation
Doxorubicin undergoes rapid metabolism in the liver. Doxorubicinol is the most common metabolite, although a substantial fraction of patients forms doxorubicin-7-deoxyaglycone and doxorubicinol-7-deoxyaglycone. There is substantial interpatient variation in biotransformation.

Elimination
About 40 to 50 % of a dose is excreted in bile within 7 days, of which about half is as unchanged active substance. Only about 5 % of a dose is excreted in urine within 5 days. Doxorubicinol, the major (active) metabolite, is excreted in both bile and urine. The elimination of doxorubicin from the blood is triphasic with mean half-lives of 12 minutes, 3.3 hours and about 30 hours.

Clearance is apparently not dose-related, but it is higher in men than in women.

Hepatic impairment
Impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Dose reduction is generally advised although there is no clear relationship between liver function tests, doxorubicin clearance and clinical toxicity.

Renal impairment
Since doxorubicin and metabolites are excreted in the urine only to a minor degree, there are no clear indications that the pharmacokinetics or toxicity of doxorubicin are altered in patients with impaired renal function.

Although renal excretion is a minor elimination pathway for doxorubicin, severe renal impairment might affect total elimination and require dose reduction.

Obese patients
In a study in obese patients (> 130 % of ideal bodyweight) the doxorubicin clearance was reduced and the half-life increased compared with a normal-weight control group. Dose adjustments might be necessary in the obese.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium chloride
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Doxorubicin should not be mixed with heparin as a precipitate may form and it should not be mixed with 5-fluorouracil as degradation may occur. Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the medicinal product.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials: 2 years

Opened vials:
The product should be used immediately after opening the vial.

Prepared infusion solutions:
Chemical and physical in-use stability at a concentration of 0.5 mg/ml has been demonstrated in sodium chloride 0.9 % and glucose 5 % for up to 7 days at 2 °C to 8 °C or room temperature (20 °C to 25 °C) when prepared in PE-bags and protected from light.
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°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Keep the vial in the outer carton in order to protect from light.
For storage conditions of the reconstituted product see section 6.3.

6.5 Nature and contents of container

Colourless glass vials (type I glass) with nominal volumes of 5 ml, 10 ml, 25 ml, 75 ml or 100 ml. Chlorobutyl rubber stoppers with ETFE layer.
Original pack containing 1 or 5 vial(s) of 5 ml / 10 ml / 25 ml / 75 ml / 100 ml (each).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Observe guidelines for handling cytotoxic medicinal products.

The following protective recommendations are given due to the toxic nature of this substance:

- Personnel should be trained in good technique for handling.
- Pregnant staff should be excluded from working with this medicinal product.
- Personnel handling doxorubicin should wear protective clothing: goggles, gowns, disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed and absorbent paper.
- All items used for administration or cleaning, including gloves, should be placed in high risk waste disposal bags for high temperature (700 °C) incineration.
- In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not graze the skin by using a scrubbing brush.
- In case of contact with eye(s), hold back the eyelid(s) and flush the affected eyes with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1 % available chlorine) solution, preferably soaking overnight and then rinse with water.
- All cleaning materials should be disposed of as indicated previously.
- Always wash hands after removing gloves.

7 MARKETING AUTHORISATION HOLDER

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