Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxorubicin 2 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 2 mg Doxorubicin hydrochloride.

Each 5 ml vial contains 10 mg of Doxorubicin hydrochloride.
Each 10 ml vial contains 20 mg of Doxorubicin hydrochloride.
Each 25 ml vial contains 50 mg of Doxorubicin hydrochloride.
Each 50 ml vial contains 100 mg of Doxorubicin hydrochloride
Each 100 ml vial contains 200 mg of Doxorubicin hydrochloride.

Excipient(s) with known effect**:** Contains sodium 3.5 mg/ml (0.15 mmol)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The product is a clear, red solution, with a pH in the range of 2.5-3.5 and osmolality between 270 mOsm/kg to 320 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxorubicin is indicated in the following neoplastic conditions.

Examples include:
- Small-cell lung cancer (SCLC)
- Breast cancer
- Advanced ovarian carcinoma
- Intravesically for bladder cancer
- 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 cytotoxic drugs.

4.2 Posology and method of administration

Doxorubicin Injection should be administered only under the supervision of a qualified physician with extensive experience in cytotoxic treatment. Also, patients must be carefully and frequently monitored during the treatment (see section 4.4)

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

Doxorubicin is administered intravenously and intravesically and must not be administered orally, subcutaneously, intramuscularly or intrathecally. Doxorubicin can be administered intravenously as bolus within minutes, as short infusion for up to an hour or as continuous infusion for up to 96 hours.

The solution is given via the tubing of a freely running intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection within 2 to 15 minutes. This technique minimises the risk of thrombophlebitis or perivenous extravasation, which can lead to severe local cellulites, vesication and tissue necrosis. A direct intravenous injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Intravenous administration:
The dosage of doxorubicin depends on dosage regimen, general status and previous treatment of the patient. Dose schedule of doxorubicin hydrochloride administration could vary according to indication (solid tumors or acute leukemia) and according to its use in the specific treatment regimen (as single agent or in combination with other cytotoxic agents or as a part of multidisciplinary procedures that include combination of chemotherapy, surgical procedure and radiotherapy and hormonal treatment).

Monotherapy
Dosage is usually calculated on the basis of body surface area (mg/m^2). On this basis, a dose of 60 - 75 mg/m^2 body surface area is recommended every three weeks when doxorubicin is used as a single agent.

Combination regimen
When doxorubicin hydrochloride is administered in combination with other antitumour agents with overlapping toxicity, such as high-dose i.v. cyclophosphamide or related anthracycline compounds such as daunorubicin, idarubicin and/or epirubicin, the dosage of doxorubicin should be reduced to 30-60 mg/m^2 every 3 – 4 weeks.

In patients, who cannot receive the full dose (eg. in case of immunosuppression, old age), an alternative dosage is 15-20 mg/m^2 body surface per week.

Intravesical administration:
Doxorubicin may be used by intravesical instillation for the treatment of superficial bladder carcinoma or in prophylaxis of tumor recurrence after transurethral resection (T.U.R) in patients with high risk of recurrence. The recommended doxorubicin hydrochloride dose for local intravesical treatment of superficial bladder tumors is instillation of 30-50 mg in 25-50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. The optimal concentration is about 1 mg/ml. Generally the solution should be retained intravesically for 1 to 2 hours. During this period the patient should be turned 90° every 15 minutes. The patient should not drink fluids for 12 hours prior to the treatment to avoid undesired dilution with urine (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.

Patients with impaired hepatic function
Since doxorubicin hydrochloride is mainly excreted via liver and bile, the elimination of the medicinal product may be decreased in patients with hepatic function impairment or bile flow obstruction and this could result in severe secondary effects.

General dose adjustment recommendations in patients with hepatic function impairment are based on serum bilirubin concentration:

Serum Bilirubin	Recommended Dose
20-50 micro mole/L	½ normal dose
> 50 micro mol/L	¼ normal dose

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

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

In order to avoid cardiomyopathy, it is recommended that the cumulative total lifetime dose of Doxorubicin (including related drugs such as daunorubicin) should not exceed 450-550mg/m^2 body surface area. If a patient with concomitant heart disease receives mediastinal **and/or heart irradiation, prior treatment with alkylating agents, and high-risk patients (with arterial hypertension since > 5 years, with prior coronary, valvular or myocardial heart damage, age over 70 years)** with a maximum total dose of 400 mg/m^2 body surface area should not be exceeded and the cardiac function of these patients should be monitored (see section 4.4).

Dose in children
Dosage in children may need to be reduced, please refer to treatment protocols and the specialist literature.

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

4.3 Contraindications

Hypersensitivity to the active substance doxorubicin hydrochloride or to any of the excipients

Contraindications for intravenous administration:
- ·Hypersensitivity to anthracendiones or other anthracyclines
- ·Marked persisting myelosuppression and/or severe stomatitis induced by previous treatment with other cytotoxic agents and/or radiation
- ·Previous treatment with maximum cumulative doses of doxorubicin and/or other anthracyclines (e.g. daunorubicin, epirubicin,idarubicin) and anthracenediones (see section 4.4).
- ·Generalized infection
- ·Severe impaired liver function
- ·Severe arrhythmias, heart failure, previous myocardial infarction, acute inflammatory heart disease
- ·Increased haemorrhagic tendency
- ·Breast-feeding (see section 4.6)

Contraindications for intravesical administration:
- ·Invasive tumors that have penetrated the bladder (beyond T1)
- ·Bladder inflammation
- ·Haematuria
- ·Difficult urinary catheter introduction (e.g. in large intravesical tumors)
- ·Breast-feeding (see section 4.6)
- ·Urinary tract infections

Doxorubicin may not be given during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Doxorubicin Injection should be administered only under the supervision of a qualified physician experienced in cytotoxic therapy for i.v. or intravesical use. Doxorubicin hydrochloride may potentiate the toxicity of other anticancer therapies. A careful control of possible clinical complications should be performed, particularly in elderly patients**,** in patients with a history of heart disease, or with bone-marrow suppression, or patients who previously have been treated with anthracyclines, or treated with radiation in the mediastinum.

Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring. It could be recommended therefore, that patients be hospitalised at least during the first phase of treatment. Doxorubicin may cause infertility during the time of drug administration.

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, SGPT, SGOT, LDH, bilirubin, uric acid.

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

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

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

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

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

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m^2 slowly increases up to the total cumulative dose of 450-550 mg/m2. Thereafter, the risk of developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2. 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), cardiotoxiciry 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. Females may be at greater risk than males. Follow-up cardiac evaluations are recommended periodically to monitor for this effect.

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

Liver function

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

Haematologic Toxicity

Doxorubicin may produce myelosuppression (See Section 4.8) Haetnatologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Dose reduction or increase of the dose interval should be considered if the blood values are not normalised. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Secondary leukaemia

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

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).

Tile intravesical route of administration should not be attempted in patients with, invasive tumours that have penetrated the bladder wall, urinary tract infections, and inflammatory conditions of the bladder.

Control of serum uric acid:

During therapy serum uric acid may increase. In case of hyperuricemia antihyperuricemic therapy should be initiated.

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

Gastrointestinal effects
An antiemetic prophylaxis is recommended.
Note: Doxorubicin should not be used in the presence in inflammations, ulcerations or diarrhoea.

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

Radiotherapy
Radiation-induced toxicities (myocardium, mucosa, skin and liver) have also been reported. 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 hydrochloride is used. Severe, sometimes fatal, hepatotoxicity (liver damage) has been reported in this connection. Prior radiation to the mediastinum increases the cardiotoxicity of doxorubicin. The cumulative dose of 400 mg/m^2 must not be exceeded especially in this case.

Infertility
Doxorubicin can have genotoxic effects. Doxorubicin may cause infertility during the time of drug administration. In women, doxorubicin may cause amenorrhea. Although ovulation and menstruation appear to return after termination of therapy, premature menopause can occur. Women should not become pregnant during and up to 6 months after treatment.

Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive measures. Also are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation (or cryo-preservation) of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with doxorubicin.

Anticancer therapies:
Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported, as with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of doxorubicin (see section 4.8).

Vaccines:
This medicinal product is generally not recommended in combination with live, attenuated vaccines. Contact to persons recently vaccinated against polio should be avoided. Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

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

Tumour-lysis syndrome:

Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumour-lysis syndrome) (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.

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

Doxorubicin hydrochloride may impart a red colour to the urine. Patients should be cautioned that this does not pose any health hazards.

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.

4.5 Interaction with other medicinal products and other forms of interactions

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

The use of trastuzumab in combination with anthracyclines (such as doxorubicin) is associated with a high cardiotoxic risk. 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. When anthracyclines are used after the end of a therapy with trastuzumab, an elevated risk of cardiotoxicity may result. The half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. If possible, there should be a sufficiently long interval (up to 27 weeks) between the end of a therapy with trastuzumab and the beginning of the anthracycline therapy. Careful monitoring of the cardiac function is imperative.

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

Doxorubicin undergoes metabolism via Cytochrome P450 (CYP450) and is a substrate for the Pgp transporter, Concomitant administration of inhibitors of CYP450 and/or Pgp might lead to increased plasma concentrations of doxorubicin and thereby increased toxicity. Conversely, concomitant administration of inducers of CYP450, such as rifampicin and barbiturates, might decrease plasma concentrations of doxorubicin and reduce efficacy.

Ciclosporin, an inhibitor of CYP3A4 and Pgp, increased the AUC of doxorubicin and doxorubicinol by 55% and 350%, respectively. The combination might require dose adjustment. Cimetidine has also been shown to reduce the plasma clearance and increase the AUC of doxorubicin.

Paclitaxel administered shortly before doxorubicin may decrease clearance and increase plasma concentrations of doxorubicin. Some data indicate that this interaction is less pronounced when doxorubicin is administered before paclitaxel.

Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while the concomitant administration of phenytoin may result in lower plasma phenytoin levels.
Elevated serum doxorubicin concentrations were reported after the concomitant administration of doxorubicin and ritonavir.

The toxic effects of a doxorubicin therapy may be increased in a combination with other cytostatics (e.g. cytarabine, cisplatin, and cyclophosphamide). Necroses of the large intestine with massive haemorrhage and severe infections may occur in connection with combination therapies with cytarabine.

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

Marked nephrotoxicity of Amphotericin B can occur during doxorubicin therapy.

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 drug. Dosing of doxorubicin must be modified if concomitant therapy with hepatotoxic drugs is mandatory.

Doxorubicin is a potent, radio sensitizing agent ("radio sensitizer"), and recall phenomena induced by it may be life-threatening. Any preceding, concomitant or subsequent radiation therapy may increase the cardiotoxicity or hepatotoxicity of doxorubicin. This applies also to concomitant therapies with cardiotoxic or hepatotoxic drugs.

Doxorubicin may cause exacerbations of hemorrhagic cystitis caused by previous cyclophosphamide therapy.

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

Doxorubicin may reduce oral bioavailability of digoxin.

During treatment with Doxorubicin patients should not be actively vaccinated and also avoid contact with recently polio vaccinated persons.

In a clinical study, an increase in doxorubicin AUC of 21% was observed when given with sorafenib 400 mg twice daily. The clinical significance of this finding is unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy
Doxorubicin has been found in foetal tissue (liver, kidney, lungs) at concentrations several times those in maternal plasma indicating that it does pass the placenta. In animals studies, doxorubicin has shown embryo-, foeto- and teratogenic effects (see section 5.3) and also proved to be highly mutagenic in the Ames test. Cytostatics should only be administered during pregnancy on strict indication, and the benefit to the mother weighed against possible hazards to the foetus.

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

Fertility
For safety reasons, men wanting a baby should preserve unexposed sperm prior to treatment with doxorubicin and abstain from engendering a child during and 6 months after therapy. Women with childbearing potential have to use effective contraception during doxorubicin therapy and 6 months after treatment.

4.7 Effects on ability to drive and use machines

Due to the frequent occurrence of nausea and vomiting, driving cars 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, septic shock, haemorrhages, tissue hypoxia or death. Nausea and vomiting as well as alopecia are seen in almost all patients.

The following adverse events have been reported in association with doxorubicin therapy:

Frequencies are defined using the following convention:
Very common (³1/10)
Common (³1/100 to <1/10)
Uncommon (³1/1,000 to <1/100)
Rare (³1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

	Common	**Uncommon**	**Rare**	**Not known**
Infections and infestations	Sepsis, septiciaemia			
Neoplasms benign and malignant			Secondary acute myeloid leukaemia when in combination with anti-neoplastic drugs which damage the DNA. (see section 4.4), tumour lysis syndrome	Acute lymphocytic leukaemia and acute myelogenous leukaemia.
Blood and lymphatic system disorders:	bone-marrow suppression, leucopenia and neutropenia			Thrombocytopenia, anaemia
Immune System disorders			Anaphylactic reactions	
Metabolism and Nutrition Disorders	Anorexia	dehydration		hyperuricaemia (see section 4.4)
Eye disorders			Conjunctivitis	keratitis and lacrimation
Cardiac disorders	cardiomyopathy, (2%: e.g. decrease of LVEF. dyspnoea);			arrhythmia, asymptomatic reduction in left ventricular ejection fraction and congestive heart failure Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. (e.g. sinus tachycardia, tachyarrhythmia, ventricular tachycardia, bradycardia, atrio-ventricular and bundle branch block). Routine ECG monitoring is recommended and caution should be exercised in patients with impaired cardiac function.
Vascular disorders		phlebitis		Thrombophlebitis; Thromboembolism; hot flushes, shock
Gastrointestinal disorders	nausea: vomiting; mucositis/stomatitis; diarrhoea,	Gastrointestinal haemorrhage, abdominal pain: ulceration of the mucous membranes in		Oesophagitis,gastric erosions, colitis hyperpigmentation of oral mucosa

		the mouth, pharynx , oesophagus and gastrointestinal tract may appear in combination with cytarabine, ulceration and necrosis of the colon, in particular the caecum, have been reported (see section 4.5)		
Respiratory, thoracic and mediastinal disorders				Bronchospasm, radiation pneumonitis
Skin and subcutaneous tissue disorder's:	alopecia	Itching, local hypersensitivity reaction of the field of radiation (recall phenomenon)	urticaria, exanthema, local erythematous reactions along the vein which was used for the injection, hyperpigmentation of skin and nails, onycholysis	tissue hypoxia, acral erythema and plantar-palmar dysaesthesia, photosensitivity
Renal and urinary disorders	local reactions (chemical cystitis) might occur at intravesical treatment (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall)			acute renal failure,
Reproductive system and breast disorders				Amenorrhoea, oligospermia, azoospermia (see section 4.4)
General disorders and administration site conditions:			anaphylactic reactions, shivering, fever, dizziness	A stinging or burning sensation at the administration site (see section 4.4)Malaise/weakness, asthenia, chills
Hepatobiliar disorders				Hepatotoxicity, transient increase of liver enzymes,
Surgical and medical procedure				Extravasation can lead to severe cellulitis, vesication and local tissue necrosis which may require surgical measures (including skin grafts) (see section 4.4)

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
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Single doses of 250 mg and 500 mg of doxorubicin have proved fatal.
Acute overdosage of doxorubicin may lead to myelosuppression (particularly leucopenia and thrombocytopenia), generally 10 - 15 days following overdose, and acute cardiac alterations, which may occur within 24 hours. Treatment includes intravenous antibiotics, transfusion of granulocytes and thrombocytes and reverse barrier nursing and treatment of heart effects. Moving the patient to a sterile room and the use of a haemopoietic growth factor should be considered.

Acute overdose with doxorubicin will also result in gastrointestinal toxic effects (mainly mucositis). This generally appears early after drug administration, but most patients recover from this within three weeks.
Chronic overdosage, with a cumulative dose exceeding 550 mg/m^2 increases the risk for cardiomyopathy and may lead to heart failure.

Delayed cardiac failure may occur up to six months after the overdosage. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances
ATC code: L01DB01

Doxorubicin is an anthracycline antibiotic. The mechanism of action is not completely elucidated. It is postulated that doxorubicin hydrochloride 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 all 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 cardiotoxic effects.

5.2 Pharmacokinetic properties

Distribution

Following intravenous injection, doxorubicin is rapidly cleared from the blood and widely distributed into tissues including lungs, liver, heart, spleen, lymph nodes, bone marrow and kidneys. The volume of distribution is about 25 litres. The degree of protein binding is 60-70%.

Doxorubicin does not cross the blood-brain barrier, although higher levels in liquor may be reached in the presence of brain metastases or leukemic cerebral dissemination. Doxorubicin is rapidly distributed into the ascites, where it reaches higher concentrations than in plasma. Doxorubicin is secreted into breast milk.

Elimination
The elimination of doxorubicin from the blood is triphasic with mean half-lives of 12 minutes (distribution), 3.3 hours and about 30 hours. Doxorubicin undergoes rapid metabolism in the liver. The main metabolite is the pharmacologically active doxorubicinol. Other metabolites are deoxyrubicin aglycone, glucuronide and sulphate conjugate. About 40 to 50% of a dose is excreted in bile within 7 days, of which about half is excreted as unchanged drug and the rest as metabolites. Only 5-15% of the administered dose is eliminated in urine.

Special populations
As the elimination of doxorubicin is mainly hepatic, impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Dose reduction is generally advised.

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

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.

In cancer patients, doxorubicin is reduced to adriamycinol, which is an active cytotoxic agent. This reduction appears to be catalysed by cytoplasmic nadph-dependent aldo-keto reductases that are found in all tissues and play an important role in determining the overall pharmacokinetics of doxorubicin.

Microsomal glycosidases present in most tissues split doxorubicin and adriamycinol into inactive aglycones. The aglycones may then undergo 0-demethylation, followed by conjugation to sulphate or glucuronide esters, and excretion in the bile.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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 drug.
Until detailed compatibility information about miscibility is available, Doxorubicin should not be mixed with other medicinal products than those mentioned under section 6.6.

6.3 Shelf life

Unopened vials: 18 months.

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

Prepared infusion solutions:
Chemical and physical in-use stability has been demonstrated in 0.9% sodium chloride injection and 5% dextrose injection for up to 28 days at 2 – 8°C and for up to 7 days at 25°C when prepared in glass containersprotected 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 condition.

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 diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

For 5 ml,
Concentrate for solution for infusion is filled in 5 ml Type - I clear tubular glass vial closed with chlorobutyl rubber stopper and aluminium flip off pink seal.

For 10 ml,
Concentrate for solution for infusion is filled in 10 ml Type - I clear tubular glass vial closed with chlorobutyl rubber stopper and aluminium flip off pink seal.

For 25 ml,
Concentrate for solution for infusion is filled in 30 ml Type - I clear molded glass vial closed with chlorobutyl rubber stopper with and aluminium flip off pink seal.

For 50 ml,
Concentrate for solution for infusion is filled in 50 ml Type - I clear molded glass vial closed with chlorobutyl rubber stopper and aluminium flip off pink seal.

For 100 ml,
Concentrate for solution for infusion is filled in 100 ml Type - I clear molded glass vial closed with chlorobutyl rubber stopper and aluminium flip off pink seal.

Pack sizes:
1 ´ 5 ml vial
1 ´ 10 ml vial
1 ´ 25 ml vial
1 ´ 50 ml vial
1 ´ 100 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Doxorubicin is a potent cytotoxic agent which should only be prescribed, prepared and administered by professionals who have been trained in the safe use of the preparation. The following guidelines should be followed when handling, preparing and disposing of doxorubicin.

Preparation
1. Personnel should be trained in good technique for handling.
2. Pregnant staff should be excluded from working with this drug.
3. Personnel handling doxorubicin should wear protective clothing: goggles, gowns, disposable gloves and masks.
4. All items used for administration or cleaning, including gloves, should be placed in high risk waste disposal bags for high temperature (700°C) incineration.

5. All cleaning materials should be disposed of as indicated previously.
6. Always wash hands after removing gloves.

Contamination
1. In case of contact with skin or mucous membrane, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not graze the skin by using a scrubbing brush. A bland cream may be used to treat transient stinging of skin.
2. 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 or normal sodium chloride 9 mg/ml (0.9%) solution for injection. Then seek medical evaluation by a physician or eye specialist.
3. In the event of spillage or leakage treat with 1% sodium hypochlorite solution or most simply with phosphate buffer (pH>8) until solution is destained. Use a cloth/sponge kept in the designate area. Rinse twice with water. Put all cloths into a plastic bag and seal for incineration.

Administration:
Intravenous (IV) administration of Doxorubicin must be very careful and it is advisable to give the medicinal product via the tubing of a freely running intravenous sodium chloride 9 mg/ml (0.9%) or dextrose 50 mg/ml (5%) within 2 to 15 minutes. This method minimizes the risk of thrombosis development and perivenous extravasation that result in severe cellulitis, vesication and tissue necrosis, and also provides rinse of the vein after the administration.

Remnants of the medicinal product as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste.

Disposal
Single use only. Any unused product or waste material should be disposed of in accordance with local requirements. Observe guidelines for handling cytotoxic drugs.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/083/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th July 2010
Date of last renewal: 24th February 2015

10 DATE OF REVISION OF THE TEXT

February 2019