Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxorubicin 50 mg Powder for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of reconstituted solution contains 2 mg doxorubicin hydrochloride.

50 mg vial:
Each vial contains 50 mg doxorubicin hydrochloride for reconstitution in 25 ml sodium chloride (0.9%) solution for injection.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Red orange lyophilized powder or plug.
pH (of reconstituted solution) = 4.5 – 6.5

The osmolality of the reconstituted solution is between 240 and 370 mOsmol/kg.

The appearance of the reconstituted solution is a clear, red coloured solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Small-cell lung cancer (SCLC)
- Breast cancer
- Recurrent ovarian carcinoma
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection (TUR)
- Systemic treatment of local advanced or metastasized bladder carcinoma
- Neoadjuvant and adjuvant therapy of osteosarcoma
- Advanced soft-tissue sarcoma in adults
- Ewing’s sarcoma
- Hodgkin’s lymphoma
- Highly malignant non-Hodgkin’s lymphoma
- Induction and consolidation therapy in acute lymphatic leukaemia
- Acute myeloblastic leukaemia
- Advanced multiple myeloma
- Advanced or recurrent endometrial carcinoma
- Wilms’ tumour (in stage II in highly malignant variants, all advanced stages [III – IV])
- 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 should be administered only under the supervision of a qualified physician with extensive experience in cytotoxic therapy. Also, patients must be carefully and frequently monitored during the treatment (see section 4.4).

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

Doxorubicin is intended for intravenous or intravesical administration only.

Intravenous administration:
Doxorubicin can be administered intravenously as bolus within minutes or as short infusion for up to an hour or as continous infusion for up to 24 hours (see also section 6.3). In monotherapy, the dose may also be divided and administered over 2-3 consecutive days. 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 extravasations, 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 (see also section 6.6).

The dosage of doxorubicin depends on dosage regimen, general status and previous treatment of the patient. Dose schedule of doxorubicin administration could vary according to indication (solid tumours or acute leukaemia) and according to its use in the specific treatment regimen (as single agent or in combination with other cytotoxic agents or as a part a 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/m2). On this basis, a dose of 60-75 mg/m2 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 antitumor 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 (e. g. in case of immunosuppression, old age) an alternative dosage is 15-20 mg/m² body surface per week.

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/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).

Hepatic impairment
In cases of decreased liver function, the dosage should be reduced according to the following table:

Serum bilirubin	Recommended dose
20-50 micro mole/l	½ normal dose
> 50-85 micro mole/l	¼ normal dose

Doxorubicin is contraindicated in patients with severe liver function disorder (>85 micromole/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.

Paediatric population
In view of the substantial risk of doxorubicin induced cardiotoxicity during childhood certain maximum cumulative dosages that depend on the youth of patients should be applied. In children (under 12 years of age) the maximal cumulative dose is usually considered 300 mg/m^2, whereas in adolescents (over 12 years of age) the maximal cumulative dose is set to 450 mg/m^2. For infants the maximal cumulative dosages are still indecisive, but even lower tolerability is assumed.
Dosage for children should be reduced, since they have an increased risk for cardiac toxicity especially late toxicity. Myelotoxicity should be anticipated, with nadirs at 10 to 14 days after start of treatment.

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

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

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

4.3 Contraindications

Hypersensitivity to doxorubicin or to any of the excipients listed in section 6.1.
Hypersensitivity to other anthracyclines or to 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, impaired cardiac function, previous cardiac infarct, acute inflammatory heart disease
- previous treatment with anthracyclines with maximum cumulative doses
- increased haemorrhagic tendency
- breastfeeding.

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
- breastfeeding.

4.4 Special warnings and precautions for use

Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

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 of the patient, 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.

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/m².

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. 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/m^2. Thereafter, the risk of developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2. 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.

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).

Gastrointestinal disorders
An antiemetic prophylaxis is recommended.
Doxorubicin should not be used in the presence of inflammation, ulceration or diarrhoea.

Haematologic toxicity
Doxorubicin may produce myelosuppression (see section 4.8). If serious myelosuppression is present, doxorubicin should not be used; a dose reduction or a delay in administration is then necessary.
Care has to be taken to ensure that a serious infection and/or episode of haemorrhage can be treated fast and effectively.
Existing infections should be treated before a therapy with doxorubicin is initiated.
Haematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophil counts return to normal values in most cases by day 21. 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. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs or when doses of the anthracyclines have been escalated. These leukaemias can have a 1 to 3 year latency period.

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.

Carcinogenesis, mutagenesis and impairment of fertility
Doxorubicin was genotoxic and mutagenic *in vitro* and *in vivo* tests and may cause infertility (see section 4.6 and section 5.3).

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.

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.

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
Vaccines are not recommended (see section 4.5). During treatment with doxorubicin hydrochloride patients should avoid contact with recently polio vaccinated persons.

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

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

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 (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

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

Doxorubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-fluorouracil, 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. If possible, there should be a sufficiently long interval (up to 22 weeks) between the end of a therapy with trastuzumab and the beginning of the anthracycline therapy. Careful monitoring of the cardiac function is imperative.

(Pre-)treatment with drugs affecting the function of the bone marrow (e.g. cytostatic agents, sulfonamides, chloramphenicol, phenytoin, amidopyrine derivates, antiretroviral drugs) might lead to severe hematopoetic disturbances. The dosage of doxorubicin has to be changed if necessary. The toxic effects of a doxorubicin therapy may be increased in a combination with other cytostatics (e.g. cytarabine, cisplatin, cyclophosphamide).
Doxorubicin hepatotoxicity may be enhanced by other hepatotoxic treatment modalities (e.g. 6-mercaptopurine).

Ciclosporin, an inhibitor of CYP3A4 and Pgp, increased the AUC of doxorubicin and doxorubicinol by 55% and 350%, respectively. A 40% dose reducton of doxorubicin is proposed for this combination.
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.

The absorption of anticonvulsants (e.g. carbamazepine, phenytoin, valproate) is decreased when administered in combination with doxorubicin.

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, cyclophosphamide). Necroses of the large intestine with massive haemorrhage and severe infections 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, 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. 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.

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

Women of childbearing potential
Doxorubicin was genotoxic and mutagenic in vitro and in vivo tests (see section 5.3).

Contraception in males and females
Men and woman who are sexually active and undergoing doxorubicin treatment should use effective contraceptive methods. Men and women should also use effective contraception up to 6 months after treatment.

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-, foeto- and teratogenic effects (see section 5.3).

Breastfeeding:
Doxorubicin has been reported to be excreted in human breast milk. A risk to the suckling child cannot be excluded. Breastfeeding should be discontinued during treatment with doxorubicin (see section 4.3).

Fertility
In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhoea (see section 4.8). 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.

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. Bonemarrow suppression is an acute dose limiting adverse effect, but is mostly transient. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death. Nausea and vomiting as well as alopecia are seen in almost all patients.

Intravesical administration may cause the following adverse reactions: hematuria, vesical and urethral irritation, stranguria and pollakisuria. These reactions are usually of moderate severity and of short duration.
Intravesical administration of doxorubicin may sometimes cause hemorrhagic cystitis; this may cause a decrease in bladder capacity.

Extravasation can lead to severe cellulitis, vesication, thrombophlebitis, lymphangitis and local tissue necrosis which may require surgical measures (including skin grafts).

The estimation of frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Infections and infestations	*Common:* sepsis, septicaemia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Uncommon:* acute lymphocytic leukaemia, acute myelogenic leukaemia *Rare:* secondary leukaemia when in combination with anti-neoplastic drugs which damage the DNA (see section 4.4), tumour lysis syndrome
Blood and lymphatic system disorders	*Very common:* myelo-suppression including leukopenia, neutropenia, thrombocytopenia, anaemia(*)
Immune system disorders	*Rare:* anaphylactic reactions
Endocrine disorders	*Very rare:* hot flashes
Eye disorders	*Rare:*

	conjunctivitis *Not known:* increased lachrymation
Cardiac disorders	*Very common:* Cardio-toxicity(**) *Common:* life-threatening congestive (dilatative) cardio-myopathy (after cumulative dose of 550 mg/m²); sinus tachycardia, ventricular tachycardia, tachy-arrhythmia, supra-ventricular and ventricular extrasystoles, bradycardia, arrhythmia; asymptomatic reduction of the left ventricular ejection fraction *Very rare:* unspecific ECG changes (ST changes, low voltage, long QT intervals); isolated cases of life-threatening arrhyth-mias; acute left ventricular failure, pericarditis, fatal pericarditis-myocarditis syndrome; atrio ventricular block, bundle branch block
Vascular disorders	*Common:* haemorrhage *Uncommon:* phlebitis *Very rare:* thrombo-embolism
Respiratory, thoracic and mediastinal disorders	*Not known:* bronchospasm, radiation pneumonitis
Gastrointestinal disorders	*Very common:* Gastro-intestinal disturbance(***) diarrhoea, nausea and vomiting; mucositis, stomatitis, oesophagitis *Common:* anorexia *Uncommon:* Gastro-intestinal haemorrhageulceration of the mucous membranes in the mouth, pharynx , oesophagus and gastro-intestinal tract may appear; in combination with cytarabine, ulceration and necrosis of the colon, in particular the caecum, have been reported (see section 4.5) *Very rare:* hyperpigmentation of the oral mucous membrane
Hepatobiliar disorders	*Not known:* hepato-toxicity (sometimes progressing to cirrhosis), transient increase of liver enzymes
Skin and subcutaneous tissue disorders	*Very common:* alopecia (dose-dependent and in most cases reversible); reddening; photo-sensitization *Common:* local hypersensitivity reactions in the field of radiation (“radiation recall reaction”); itching *Rare:* urticaria, exanthema, hyperpigmentation of skin and nails, onycholysis;

	extravasation (may lead to severe cellulites, vesication, thrombophlebitis, lymphangitis, and local tissue necrosis) *Very rare:* acral erythemas; blistering; palmar-plantar erythrodysaesthesia *Not known:* actinic keratosis
Musculoskeletal and connective tissue disorders	*Not known:* Arthralgia
Renal and urinary disorders	*Very common:* red coloration to the urine *Common:* dysuria chemical cystitis following intravesical administration (with dysuric complaints such as vesical irritation, urethral irritation, dysuria, stranguria, pollakisuria, haematuria, vesicular spasms, hemorrhagic cystitis) *Very rare:* acute renal failure (isolated cases); hyper-uricaemia and subsequent uric acid nephropathy as a consequence of massive tumour lysis
Reproductive system and breast disorders	*Very rare:* Amenorrhoea; oligo-spermia; azoo-spermia
General disorders and administration site conditions	*Very common:* Fever *Uncommon:* dehydration *Rare:* shivering, dizziness; injection site reactions (local erythematous reactions along the vein, pain, phlebitis, phlebosclerosis) *Not known:* malaise/weakness
Surgical and medical procedure	*Not known:* radiation damage (skin, lungs, oesophagus, gastro-intestinal mucosa, heart) that is already healing may reappear following doxorubicin administration

(*) Myelosuppression is one of the dose-limiting side-effects and may be serious. It manifests mainly in the decrease of the leukocyte count. Leucopenia was observed in almost 75% of the patients with an adequate bone marrow reserve who were treated with 60 mg/m² BSA every 21 days. Although less frequently, thrombocytopenia, neutropenia, and anaemia were also reported. Superinfections (very frequent) and haemorrhage were likewise observed in a connexion with the appearance of bone marrow suppression. Myelosuppression usually culminates 10 to 14 days after the administration of doxorubicin and subsides between the 21st and 28th day in most cases. If appearing, thrombocytopenia or anaemia occurs in the same period, but is usually less severe. (See section 4.4).

(**) Doxorubicin is cardiotoxic. The risk that the cardiotoxic side-effects become manifest is elevated during and after radiation therapy of the mediastinal region, after a pre-treatment with potentially cardiotoxic agents (e.g. anthracyclines, cyclophosphamide), and in elderly patients (over 60 years) and patients with manifest arterial hypertension. (See section 4.4).

The cardiotoxic effect of doxorubicin can manifest in two types:

Acute type
The acute-type side-effects occur mostly within the first 24 to 48 hours after initiation of therapy, are not dosedependent and are characterized by the following symptoms: temporary arrhythmia (frequent), especially sinus tachycardia (frequent), and supraventricular and ventricular extrasystoles. They are (very rarely) characterized by unspecific ECG changes (ST changes, low voltage, and long QT intervals).
These changes are generally reversible, and their appearance is no contraindication for the repeated use of doxorubicin. However life-threatening arrhythmias may occur during, or few hours after the use of doxorubicin; in isolated cases, acute left ventricular failure, pericarditis or fatal pericarditis-myocarditis syndrome was reported.

Delayed type
The delayed-type side-effects are manifestations of dose-dependent cumulative organ toxicity, which is generally irreversible and often life-threatening. They often manifest as congestive (dilatative) cardiomyopathy with the signs of left ventricular failure within few months of the termination of therapy. Cardiotoxicity may, however, become manifest for the first time as late as several years after the termination of the therapy; its incidence increases with the total cumulative dose. (See section 4.4).

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

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

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

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

A haemodialytic therapy is probably useless in intoxications with doxorubicin because doxorubicin has a very large volume of distribution and only 5% of a dose is eliminated by the kidneys.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents and anthracyclines and related substances
ATC code: L01D B01

Doxorubicin is an anthracycline antibiotic. The mechanism of action is not completely elucidated. It is postulated that Doxorubicin Agila 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 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 l/kg. 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.

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

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.

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

Lactose monohydrate

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.

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

6.3 Shelf life

Vial before opening:
2 years.

Reconstituted solution
Chemical and physical in-use stability following reconstitution in 0.9 % sodium chloride solution has been demonstrated for 7 days at 25°C and 15 days at 2-8°C.
From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place under controlled and validated aseptic conditions.

Reconstituted solution further diluted in 0.9% sodium chloride solution
The chemical and physical in-use stability after dilution to a concentration of 0.1mg/ml to 1.0mg/ml has been demonstrated for 24 hours when stored protected from light at 2-8°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place under controlled and validated aseptic conditions.

Reconstituted solution further diluted in 5% Glucose solution
The chemical and physical in-use stability after dilution to a concentration of 0.1mg/ml to 1.0mg/ml has been demonstrated for 24 hours when stored protected from light at 2-8°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place under controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I flint tubular glass vials, stoppered with a dark grey bromobutyl rubber stopper and sealed with an electric blue flip off aluminium seal.
Trade package quantities: Boxes with one vial of 50 mg doxorubicin hydrochloride.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

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 reconstituted solution is a clear, red coloured solution.

Further dilution of the appropriate volume of the reconstituted solution with either of 0.9 % sodium chloride solution or 5 % glucose solution is required to a final concentration of between 0.1 mg/ml and 1 mg/ml.

For recommendation on posology and method of administration see section 4.2.
For single use only.

The following guidelines should be followed when handling, preparing and disposing of doxorubicin.

Preparation
1. Cytotoxic agents should be prepared for administration only by personnel who have been trained in the safe handling of such preparations. Refer to local cytotoxic guidelines before commencing.
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 eye(s) with copious amounts of water for at least 15 minutes or normal sodium chloride 9 mg/ml (0.9%) solution for injection. Seek medical evaluation by a physician or eye specialist.
3. In the event of spillage or leakage treat with 1% sodium hypochlorite solution or phosphate buffer (pH>8) until solution is decoloured. Use a cloth/sponge kept in the designated area. Rinse twice with water. Put all cloths into a plastic bag and seal for incineration.

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

Generics (UK) Limited
Station Close
Potters Bar
Hertfordshire EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0405/097/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th March 2015

10 DATE OF REVISION OF THE TEXT

January 2016