Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxorubicin 2mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxorubicin hydrochloride

1ml contains 2 mg Doxorubicin hydrochloride.

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

Excipients: The product contains sodium chloride (3.54 mg sodium per 1 ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Red concentrate for infusion. pH = 2.5 – 3.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer, sarcoma, small-cell carcinoma of the lung, Hodgkin disease or non-Hodgkin lymphoma, acute leukaemia, cancer of the thyroid, bladder, ovaries, Paediatric tumours, such as neuroblastoma.
Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs.

4.2 Posology and method of administration

Treatment with Doxorubicin should be started by or after consulation with a doctor with extensive experience from cytostatic treatment.
The concentrate is injected via the tubing of a freely-running intravenous infusion (Sodium chloride 0.9% intravenous infusion or Dextrose 5% intravenous infusion) over 2-15 minutes. This technique minimizes the risk of thrombophlebitis or perivenous extravasation which can lead to severe cellulitis and vesication.
Intravenous administration: The dosage of doxorubicin depends on dosage regimen, general status and previous treatment of the patient.
Several dosage regimens exist: The recommended dose is 60-75 mg/m^2 body surface i.v. as a single dose or in divided doses on 2-3 consecutive days administered with 21 day's intervals. The lower dose should be given to patients with bone marrow depression.
When Doxorubicin is administered in combination with other cytostatics, the dosage should be reduced to 30-60 mg/m^2.
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**.**
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; 450 mg/m^2 should not be exceeded in cases of previous radiation of mediastinum, previous or concomitant treatment with potentially cardiotoxic agents.
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	50% normal dose
> 50 micro mole/L	25% normal dose

In cases of renal insufficiency with a GFR less than 10 ml/min, 75% of the calculated dose should be administered.
Dosage in children may need to be reduced, please refer to treatment protocols and the specialist literature.
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 solution should remain in the bladder for 1-2 hours.
During this period the patient should be turned 90^{o} 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.
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).

A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Intravesical instillation is contraindicated in invasive bladder tumours.

4.3 Contraindications

Hypersensitivity to doxorubicin, other anthracyclines or anthracenediones
Contraindications for intravenous administration:
-remaining myelosuppression or severe stomatitis which appeared during previous cytotoxic treatment
-general infection
-severe impaired liver function
-severe arrhythmia, impaired heart function, previous cardiac infarct
-previous treatment with anthracyclines with maximal cumulative doses

Contraindications for intravesical administration:
-invasive tumours that have penetrated the bladder (beyond T1)
-urinary tract infections
-inflammation of the bladder
-problems with catheterisation
Doxorubicin may not be given during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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.
Control of blood values: Before every treatment cycle total and differential leukocyte count, erythrocyte and thrombocyte counts should be performed. Bone-marrow suppression induced by Doxorubicin, primarily affecting the leukocytes, requires a thorough haematological monitoring since severe myelosuppression may lead to superinfections and bleedings. Severe leucopoenia may appear at doses recommended for treatment of solid tumours (a number of leukocytes of 1 000/mm3 or lower is expected during full dose treatment with Doxorubicin). The leucopoenia is most pronounced 10 – 14 days after the treatment and leukocytes have in most cases returned to normal at day 21.
Control of heart function: There is a known risk of development of anthracycline induced cumulative dose-dependent cardiomyopathy. Therefore a cumulative dose of (450-)550 mg/m^2 should not be exceeded. At doses above this, the risk of development of heart failure considerably increases. The heart function should therefore be assessed before start of the treatment and carefully monitored during the whole treatment. Electrocardiography before and after each treatment cycle is recommended. Changes in ECG such as depression or negative T-wave, decrease in the ST-segment or arrhythmias are usually

signs of an acute but transient (reversible) toxic effect and are not considered indications for suspension of doxorubicin therapy. However, a reduction in the amplitude of the QRS-wave and a prolongation of the systolic interval are considered more indicative of anthracycline-induced cardiac toxicity. The best sign to predict cardiomyopathy is a reduction in the left ventricular ejection fraction (LVEF), determined by ultrasound or heart scintigraphy. LVEF-investigations should be performed before treatment and be repeated after each accumulated dose of about 100 mg/m^2, and at clinical signs of heart failure. As a rule, an absolute decrease with $\geq$10 % or a decrease below 50 %, in patients with normal initial LVEF-values, is a sign of an impairment of the heart function. Continued treatment with doxorubicin must in these cases be carefully evaluated. The risk for cardiotoxicity may increase in patients previously on radiotherapy towards the mediastinal pericardium, in patients previously treated with other anthracyclines and/or anthracenediones, or in patients with a history of heart diseases. The total dose of doxorubicin administered to the individual patient should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents such as high-dose i.v. cyclophosphamide, mediastinal irradiation or related anthracycline compounds such as daunorubicin.
Control of liver function: Doxorubicin is mainly eliminated via the hepatobiliary system. The elimination of the drug can therefore be prolonged with subsequent general toxicity if the liver function is impaired or biliary secretion is obstructed. Before start and during treatment, control of the liver function with conventional tests such as AST, ALT, ALP and bilirubin is recommended. Dose reduction may be necessary (see 4.2).
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).
Doxorubicin may potentiate the toxicity of other anticancer chemotherapies (see section 4.5). Doxorubicin amplifies the radiation toxicity to heart muscle, mucous membranes, skin and liver.
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.
The patient should be informed that the urine might be reddish after administration.

This medicinal product contains 3.54 mg sodium per 1 ml of doxorubicin hydrochloride concentrate for 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

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.

Doxorubicin hepatotoxicity may be enhanced by other hepatotoxic treatment modalities (e.g. 6-mercaptopurine).
Doxorubicin used in combination with ciclosporin might require dose-adjustment. At concomitant administration of ciclosporin, the clearance of doxorubicin is reduced by approximate 50%. The doxorubicin AUC is increased by 55% and AUC of doxorubicinol by 350%. With this combination a 40% dose reduction of doxorubicin is suggested. Ciclosporin inhibits, similar to verapamil, both CYP3A4 and P-glycoprotein, which might explain the interaction and resulting in an increase in adverse effects.
Cimetidine also reduced the plasma clearance and increased the AUC of Doxorubicin, possibly by similar mechanisms as suggested for ciclosporin, and may thus lead to an increase in adverse effects. Conversely, phenobarbital decreased Doxorubicin plasma levels and may thus lead to a decrease in efficacy.
Doxorubicin potentiates the effect of radiation therapy and can, even if administered some considerable time after discontinuation of the radiation therapy, cause severe symptoms in the area concerned.
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.

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-, foeto- and teratogenic effects (see 5.3 Preclinical safety data).Men and women should use effective contraception during and up to 6 months after treatment.

Lactation:
Doxorubicin has been reported to be excreted in human breast milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with doxorubicin.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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.

Common
Cardiac disorders: Cardiomyopathy (2%; e.g. decrease of LVEF, (≥1/100 to dyspnoea), ECG changes (e.g. sinus tachycardia, tachyarythmia, <1/10) ventricular tachycardia, bradycardia, bundle branch block)

Blood and lymphatic system disorders: Bone-marrow suppression
Gastrointestinal disorders: Nausea, vomiting, mucositis, anorexia, diarrhoea

Renal and urinary disorders: Local reactions (chemical cystitis) might occur at intravesical treatment

Skin and subcutaneous tissue disorders: Alopecia

Uncommon
Gastrointestinal disorders: In combination with cytarabine ulceration (≥ 1/1,000 to and necrosis of the colon, in particular the caecum, have been <1/100) reported.

Rare
Eye disorders: Conjunctivitis (≥1/10,000 to <1/1,000)

Skin and subcutaneous tissue disorders:
Urticaria, exanthema, local erythematous reactions along the vein which was used for the injection, hyperpigmentation of skin and nails**,** onycholysis *General disorders and administration site conditions*: Anaphylactic reactions, shivering, fever, dizziness

Blood and lymphatic system disorders:
Maximal bone-marrow suppression occurs after 10-14 days, but the white and red blood cell counts (blood values) are often normalised after 21 days. Dose reduction or increase of the dose interval should be considered if the blood values are not normalised. Haematological monitoring should be undertaken regularly in both haematological and non-haematological conditions. Secondary acute myeloid leukaemia (AML), with or without a pre-leukaemic phase, has in rare cases been reported in patients simultaneously treated with doxorubicin and antineoplastic drugs, which damage the DNA. These cases might have a short latency period, 1-3 years.

Cardiac disorders: Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. Cardiomyopathy can develop even long after discontinuation of the treatment, and is of serious nature. It is often characterised by a decrease in LVEF, a decrease in amplitude of the QRS wave, rapid onset of cardiac dilatation, which often does not respond to treatment with medicinal products with inotropic effect. Acute transient ECG changes that occur directly in connection with, or a few hours after the administration, are in most cases reversible and are usually of no clinical significance.

Gastrointestinal disorders: Nausea and vomiting often occur during the first 24 hours after the administration. Mucositis (stomatitis and oesophagitis) may occur 5-10 days after administration, and is more frequent and serious when a therapy, which involves treatment during three consecutive days, is applied. Ulceration and necrosis of the colon, in particular the caecum, resulting in bleeding and serious infections, sometimes fatal, have been reported in patients with acute non lymphocytic leukaemia, who, during three days, were treated with doxorubicin in combination with cytarabine. Hyperpigmentation of oral mucosa also occurred.

Skin and subcutaneous tissue disorders: Alopecia is dose-dependent and in most cases reversible. Photosensitization, "radiation recall reaction". Extravasation can lead to severe cellulitis, vesication and local tissue necrosis which may require surgical measures (including skin grafts).

Other side effects:
Hyperuricaemia, bronchospasm, amenorrhoea, transient increase of liver enzymes.

4.9 Overdose

Acute overdosage of doxorubicin may lead to myelosuppression (particularly leucopoenia 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: L01D B01 Anthracyclines and related substances
Doxorubicin belongs to the group of anthracyclines and is a cytostatic antibiotic that has been isolated from cultures of *Streptomyces peucetius var. caesius*. It is now prepared semi-synthetically from daunorubicin. Doxorubicin is a strong tissue irritant.
The biological activity of doxorubicin is attributed to its DNA-binding property, which results in inhibition of the enzymatic system, vital for the DNA-replication and the DNA-transcription. The blocking of the cellular cycle seems to be maximal during S phase and mitosis, but inhibition has also been observed during other cell cycle phases.

5.2 Pharmacokinetic properties

After intravenous administration, doxorubicin elimination is characterised by a tri-phasic elimination from plasma with a terminal half life of approximately 30 hours. The distribution volume is approximately 25 L/kg. The degree of protein binding in plasma is approximately 70%.
Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bone-marrow. Doxorubicin does not cross the blood-brain barrier.
Doxorubicin is rapidly metabolised, and the main metabolite is the less active 13 dihydroderivative doxorubicinol. Within five days approximately 5% is recovered in the urine, whilst 40-50% is excreted through the bile within 7 days. Reduced liver function results in a slower elimination of the substance.

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

Hydrochloric acid
Sodium chloride

Water for injections

6.2 Incompatibilities

Doxorubicin must not be mixed with heparin, as this will result in precipitation. Until detailed compatibility information about miscibility is available, Doxorubicin should not be mixed with any other medicinal products.
Incompatibilities with the following products have also been reported: Aminophyllin, cephalotin, dexamethasone, fluorouracil, hydrocortisone.

6.3 Shelf life

Unopened vial: 18 months
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

From a chemical and physical point of view, the product should be used immediately after first opening. Any unused portion must be discarded after use.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC)
Keep vial in the outer carton in order to protect from light
Store in an upright position

6.5 Nature and contents of container

Colourless, borosilicate, type I glass vial with chlorobutyl based, teflon layered, type I rubber stopper and aluminium cap with plastic flip-off top, containing 5ml, 10ml, 25ml, 50ml or 100ml of sterile solution of Doxorubicin hydrochloride 2 mg/ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

Doxorubicin is compatible with sodium chloride 0.9% and dextrose 5%.

Guidelines for the safe handling and disposal of antineoplastic agents:
1. Adequate protective disposable gloves, goggles, gown and mask should be worn.
2. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 0.9% sodium chloride solution. Then seek medical evaluation by a physician.
3. In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Always wash hands after removing gloves.
4. Spillage or leakage should be treated with diluted sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water or most simply with phosphate buffer (pH>8) until the solution is destained. All cleaning materials should be disposed of as detailed below.
5. Pregnant staff should not handle the cytotoxic preparation.
6. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Seacross Pharma (Europe) Limited, POD 13, The Old Station House, 15A Main Street, Blackrock Dublin, A94 T8P8 Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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