

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxorubicin 2 mg/ml solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 2 mg doxorubicin hydrochloride.

Excipient with known effect:

9 mg/ml sodium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear red solution for injection. 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 2 mg/ml solution for injection should be started by or after consultation with a doctor with extensive experience from cytostatic treatment.

The solution is injected via the tubing of a freely-running 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/m² 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 2 mg/ml solution for injection is administered in combination with other cytostatics, the dosage should be reduced to 30-60 mg/m².

In patients, who cannot receive the full dose (eg. 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; 450 mg/m² 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 | ½ normal dose |
| > 50 micro mole/L | ¼ normal dose |

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

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

Intravesical administration:
Doxorubicin 2 mg/ml solution for injection 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 90⁰ 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 4.4 Special warnings and precautions for use*).

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 (*see 4.4 Special warnings and precautions for use*).

4.3 Contraindications

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

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

- Contraindications for intravesical administration:*
- o invasive tumours that have penetrated the bladder (beyond T)
 - o urinary tract infections
 - o inflammation of the bladder
 - o 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 2 mg/ml solution for injection, primarily affecting the leukocytes, requires a thorough haematological monitoring since severe myelosuppression may lead to superinfections and bleedings. Severe leucopenia may appear at doses recommended for treatment of solid tumours (a number of leukocytes of $1\,000/\text{mm}^3$ or lower is expected during full dose treatment with Doxorubicin 2 mg/ml solution for injection). The leucopenia 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 $(450\text{--}550)\text{ mg/m}^2$ 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 section 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 2 mg/ml solution for injection 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.

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-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.

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

Doxorubicin 2 mg/ml solution for injection 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 2 mg/ml solution for injection 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*).

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.

Fertility

Men and woman should use effective contraception during and up to 6 months after treatment.

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
(≥1/100 to
<1/10)

Cardiac disorders: Cardiomyopathy (2%; e.g. decrease of LVEF, dyspnoea), EEG changes (e.g. sinus tachycardia, tachyarrhythmia, ventricular tachycardia, bradycardia, bundle branch block)

Blood and lymphatic system disorders: Bone-marrow suppression

Gastrointestinal disorders: Nausea, vomiting, mucositis, anorexia, diarrhea

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

Skin and subcutaneous tissue disorders: Alopecia

Uncommon
($\geq 1/1,000$ to
<1/100)

Gastrointestinal disorders: In combination with cytarabine ulceration and necrosis of the colon, in particular the caecum, have been reported.

Rare
($\geq 1/10,000$ to
<1/1,000)

Eye disorders: Conjunctivitis

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 anti-neoplastic 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.

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 preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option.

FREEPOST

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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/m² 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

Pharmacotherapeutic group: anthracyclines and related substance, ATC code: L01D B01

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 2 mg/ml solution for injection must not be mixed with heparin, as this will result in precipitation. Until detailed compatibility information about miscibility is available, Doxorubicin 2 mg/ml solution for injection should not be mixed with other medicinal products except those mentioned in section 6.6.

Incompatibilities with the following products have been reported:
Aminophyllin, cephalotin, dexamethasone, fluorouracil, hydrocortisone.

6.3 Shelf life

Shelf life before opening: 3 years.

Shelf life after dilution:

Chemical and physical in-use stability after dilution in physiological saline solution or glucose solution for infusion 50 mg/ml has been demonstrated for 7 days when stored protected from light in a refrigerator and for 1 day when stored not protected from light at room temperature.

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 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions after dilution of the medicinal product, *see section 6.3*.

6.5 Nature and contents of container

Clear vials (glass type I) with chlorobutyl stopper and aluminium cap with plastic flip-off top.
Package sizes: 5 ml, 25 ml and 75 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Doxorubicin can also be administered as intravenous infusion in physiological saline or glucose solution for infusion 50 mg/ml.

Personnel should be trained in good technique for handling cytotoxic drugs. Pregnant staff should be excluded from working with this drug. Personnel handling this, and all cytotoxic drugs, should wear protective clothing: goggles, gowns and disposable gloves and masks.

If Doxorubicin 2 mg/ml solution for injection comes in contact with skin or mucous membranes, the exposed area should be thoroughly washed with soap and water. If the substance gets into the eyes, rinse with water or sterile physiological saline, whereupon an eye specialist should be consulted.

After use, bottles and injection materials, including gloves, should be destructed according to the rules for cytostatics.

Inactivation of spilled or leaked drug can be obtained with 1% sodium hypochlorite solution or most simply with phosphate buffer (pH>8) until solution is destained. All cleaning materials should be disposed of as indicated previously.

7 MARKETING AUTHORISATION HOLDER

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Stadastraße 2-18
61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1070/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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