

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxorubin 50 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxorubin, powder for solution for injection contains 50 mg of doxorubicin hydrochloride EP.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

In combination with other antineoplastic drugs, doxorubicin is intended for the treatment of acute lymphocytic leukaemia, (except acute lymphatic leukaemia of low risk in children), acute myeloid leukaemia, Hodgkin- and non-Hodgkin lymphomas, osteosarcoma, Ewing sarcoma, adult soft tissue sarcoma, metastatic breast carcinoma, gastric carcinoma, small-cell lung cancer, neuroblastoma, Wilms tumour and bladder carcinoma.

Doxorubicin may be used intravesically as single agent for treatment and prophylaxis of superficial bladder carcinoma.

4.2 Posology and Method of Administration

The route of administration is by intravenous injection.

The vial contents must be reconstituted before use with water for injection or normal saline (see Section 6.6 Instructions for Use/Handling).

Doxorubicin should **not** be administered intramuscularly or subcutaneously.

Intravenous administration

Doxorubicin may be given by intravenous bolus injection, or as continuous infusion. Bolus injection causes higher peak plasma concentration and therefore is probably more cardiotoxic. Intravenous administration occurs preferably through a running, recently applied intravenous infusion, of sodium chloride injection, dextrose injection 5% or sodium chloride and dextrose injection over 3 to 5 minutes.

Patients with an increased risk for cardiotoxicity (see section 4.4 Special warnings and precautions for use) should be considered for treatment with a 24 hours continuous infusion, rather than bolus injection. In this way, cardiotoxicity may be less frequent, without a reduction in therapeutic efficacy. In these patients, the ejection fraction should be measured before each course.

Adults

Dosage depends on tumour type, hepatic function, and concurrent chemotherapy.

The commonly recommended dosage schedule as single agent is 60-75 mg/m² by intravenous injection, once every 3 weeks. An alternative dose schedule is 20 mg/m² intravenously, during 3 consecutive days, once every 3 weeks.

Lower doses may be required in patients with inadequate marrow reserves and in patients who have had prior treatment with other cytotoxic agents. When used in combination with other chemotherapeutic agents the dosage of 30-60 mg/m² are administered. Myelosuppression may be more pronounced because of the additive effect of the drugs.

The risk of development of cardiomyopathy gradually increases with the dosage. The maximum cumulative dose of 450 mg/m² should not be exceeded. The administration of doxorubicin should be monitored by electrocardiography, echocardiography and carotid pulse curve: When the voltage of the QRS wave decreases by 30% or at a fractional shortening of 5% it is recommended to stop treatment.

If a patient receives mediastinal irradiation, has concomitant heart disease, or is also treated with other cardiotoxic, non-anthracycline oncolytics, a maximal cumulative dose of 400 mg/m² is recommended.

Doxorubicin dosage should be reduced if the bilirubin is elevated. When bilirubin is 12 to 30 mg/l - half the dosage should be given; when bilirubin concentrations > 30 mg/l, one quarter of the dosage should be given.

In general, impaired renal function does not require dose reduction.

Children

Dosage for children may be lowered, since they have an increased risk for late cardiotoxicity. Myelotoxicity should be anticipated, with nadirs at 10 to 14 days after start of treatment, but is usually followed by a rapid recovery due to the large bone marrow reserve of children as compared to adults.

Superficial Bladder Carcinoma And Bladder Carcinoma In Situ

The recommended dosage is 50 mg in 50 ml normal saline, administered via a sterile catheter. Initially, this dose is given weekly, later on monthly. The optimal duration of treatment has not yet been determined; it ranges from 6 to 12 months.

Restrictions regarding the maximal cumulative dose, as with intravenous administration, do not apply to intravesical administration, because systemic absorption of doxorubicin is negligible.

4.3 Contra-Indications

Doxorubicin therapy should not be started in the following cases:

- Marked myelosuppression induced by previous chemotherapy or by radiotherapy.
- Pre-existing heart disease.
- Previous treatment with complete cumulative doses of doxorubicin or other anthracyclines.
- Doxorubicin should not be used intravesically for the treatment of bladder carcinoma in patients with urethral stenosis who cannot be catheterised.

4.4 Special Warnings and Precautions for Use

General precautions

Doxorubicin should only be used under supervision of a physician who is experienced in cytotoxic therapy.

Nausea, vomiting and mucositis are often severe and should be treated appropriately.

Doxorubicin should **not** be administered intramuscularly or subcutaneously.

The total dose of doxorubicin administered to the individual patient should take into account any previous or concomitant therapy with related compounds such as daunorubicin.

Extravasation

Extravasation results in a severe and progressive tissue necrosis. If extravasation occurs, the injection should be terminated immediately and restarted in another vein. Flooding with normal saline, local infiltration with corticosteroids with or without sodium hydrogen carbonate solution (8.4%), and application of dimethylsulfoxide have been reported with varying success. The advice of a plastic surgeon should be sought, and wide excision of the involved area should be considered.

Cardiotoxicity

Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of doxorubicin therapy. Severe cardiac failure may occur precipitously without antecedent ECG change.

The risk of severe, irreversible and therapy-resistant cardiomyopathy and resulting congestive heart failure gradually increases with increasing dosages. A cumulative dose of 450 mg/m² should not be exceeded.

Age over 70 or below 15 years and female gender in children should be considered a risk factor, as well as concomitant heart disease. In addition, ECG changes may occur including a reduction in the voltage of the QRS wave, and a prolongation of the systolic time interval, and the ejection fraction may be reduced.

In patients previously treated with other anthracyclines or cyclophosphamide, mitomycin C or dacarbazine, and patients who received radiotherapy to the mediastinal area, cardiotoxicity may occur at doses lower than the recommended

cumulative limit. The concurrent use of trastuzumab and anthracyclines (like doxorubicin) is not recommended (see section 4.5).

Acute severe arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

Heart function should be assessed before, during and after doxorubicin therapy, e.g., by ECG, echocardiography or determination of the ejection fraction. If test results indicate change in cardiac function associated with doxorubicin the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Myelosuppression

The high incidence of bone marrow depression requires careful haematologic monitoring. The nadir is reached between 10-14 days after administration. Blood values usually return to normal within 21 days after administration. Doxorubicin therapy should not be started or continued when polynuclear granulocyte counts are below 2000/mm³, except in the treatment of acute leukaemia, where lower limits may be applied, depending on the circumstances.

Careful haematologic monitoring is also required because of the risk of secondary leukaemias after treatment with cytotoxic agents (see section 4.8 “Undesirable effects”). A remission of acute leukaemia can be achieved when detected at an early stage.

Hepatic impairment

Hepatic function (SGOT, SGPT, alkaline phosphatase and bilirubin) should be evaluated before and during therapy.

Hyperuricaemia

Doxorubicin may induce hyperuricemia.

The blood uric acid level should be monitored. Sufficient fluid intake should be ascertained (with a daily minimum of 3 l/m²). If necessary, a xanthine-oxidase inhibitor (allopurinol) may be administered.

Discoloration of urine

Doxorubicin may impart a red coloration to the urine.

4.5 Interactions with other Medicaments and other forms of Interaction

Doxorubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, mitomycin C, dacarbazine, dactinomycin and, possibly, cyclophosphamide. Also the risk of cardiotoxicity is increased if trastuzumab is given with or after doxorubicin. Trastuzumab and anthracyclines should not be used concurrently in combination except in a well-controlled clinical trial setting with cardiac monitoring. Furthermore, paclitaxel decreases the elimination of doxorubicin. Care should be taken in case of co- administration of both drugs, because of an increased risk of cardiotoxic effects of doxorubicin. The severity of neutropenia or stomatitis may also be increased.

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

Doxorubicin may enhance the hepatotoxicity of 6-mercaptopurine.

The effects of radiation may be enhanced, and recall of these reactions may occur with doxorubicin therapy, even some time after termination of radiotherapy.

Inducers of the enzyme cytochrome P-450 (e.g. rifampicin and barbiturates) may stimulate the metabolism of doxorubicin, with a possible decrease in efficacy.

Inhibitors of cytochrome P-450 (e.g. cimetidine) may decrease the metabolism of doxorubicin, with a possible increase in toxic effects.

4.6 Pregnancy and Lactation

Clinical evidence suggests a possible adverse effect on the foetus. In animals doxorubicin has embryotoxic and teratogenic effects.

Doxorubicin is excreted into breast milk. Usage during pregnancy and lactation is therefore not recommended.

Men as well as women should take effective contraceptive measures during and for at least three months after doxorubicin 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

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity.

Blood and Lymphatic System Disorder

Myelosuppression includes a transient leucopenia very commonly. Anaemia and thrombocytopenia are less common. Myelosuppression reaches its nadir at 10 to 14 days after treatment. Blood levels usually return to normal within 21 days after administration.

Myelodysplastic syndrome and acute myeloid leukaemia have been observed after treatment with combination therapy including doxorubicin. With topoisomerase II inhibitors, secondary leukaemias have been reported more frequently than expected in the form of acute myeloid leukaemia classification 2, 3, and 4. These forms of leukaemia can have a short period of latency (1 to 3 years) but much longer periods have been reported. They can be cured when detected at an early stage and with an appropriate curative treatment (see section 4.4 "Special warnings and special precautions for use").

Immune Disorder

Hypersensitivity reactions, such as fever, urticaria and anaphylaxis occur rarely.

Doxorubicin influences and potentiates normal tissue reactions to radiation. Also, late

(“recall”) reactions may occur when doxorubicin is administered some time after irradiation. Facial flushing may occur if the injection is given too rapidly.

Cardiac Disorder

Cardiotoxicity may occur as arrhythmia directly following drug administration; ECG changes, including T-wave flattening and S-T depression, may last up to 2 weeks after administration.

The risk of cardiomyopathy increases with an increasing dosage. Severe cardiotoxicity is more likely after high cumulative doses of doxorubicin (see section 4.4 Special Warnings and Precautions for Use) and may occur months or years after administration.

Gastrointestinal Disorder

Nausea and vomiting are very common and diarrhoea occurs occasionally.

Mucositis (stomatitis or oesophagitis) may occur 5 to 10 days after administration.

Hepato-biliary Disorder

Slight transient increases of liver enzymes have been reported. Concomitant irradiation of the liver may cause severe hepatotoxicity, sometimes progressing to cirrhosis.

Other adverse reactions:

A generally reversible alopecia is very common.

A red colouration of the urine, imparted by doxorubicin, is very common.

Thrombophlebitis and conjunctivitis have been reported.

Doxorubicin may induce hyperuricemia.

Intravesical Administration

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

4.9 Overdose

Acute overdose of doxorubicin enhances the toxic effects, particularly-mucositis, leucopenia and thrombocytopenia. Overdose of intravesical administration may result in more severe cystitis. Treatment of acute overdose consists of treatment of the severely myelosuppressed patient with hospitalisation, antibiotics and transfusions after consultation of an oncologist.

Chronic overdosage with cumulative doses exceeding 450 mg/m² increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. Single doses of 250 mg and 500 mg of doxorubicin have proved fatal. Such doses may cause acute myocardial degeneration within 24 hours and severe myelosuppression, the effects of which are greatest between 10 and 15 days after administration. Treatment should be symptomatic and supportive. Delayed cardiac failure may occur up to six months after the overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Doxorubicin is an oncolytic drug of the anthracycline group. It is isolated from cultures of *Streptomyces peucetius* var. *caesius*. Animal studies have shown an oncolytic action in several solid and haematologic tumours. The mechanism of action is not completely elucidated. A major mechanism is probably inhibition of topoisomerase II, resulting in DNA breakage. Intercalation and free-radical formation is probably of minor importance. Drug resistance, due to increased expression of the MDR-1 gene encoding for a multidrug efflux pump, has been reported regularly.

5.2 Pharmacokinetic Properties

The intravenous administration of doxorubicin is followed by a rapid plasma clearance ($t_{1/2} \sim 10$ min.) and significant tissue binding. The terminal half-life is approximately 30 hours.

Doxorubicin is partly metabolised, mainly to doxorubicinol and to a lesser extent, to the aglycone, and is conjugated to the glucuronide and sulphate. Biliary and faecal excretion represents the major excretion route. About 10% of the dose is eliminated by renal excretion. Plasma protein binding of doxorubicin ranges from 50-85%. The volume of distribution is 800-3500 l/m².

Doxorubicin is not absorbed after oral administration; it does not cross the blood-brain barrier.

Impairment of liver function may decrease the clearance of doxorubicin and its metabolites.

5.3 Preclinical Safety Data

There are no preclinical safety data of relevance to the prescriber which are additional to those already mentioned in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose

6.2 Incompatibilities

Doxorubicin should not be mixed with other drugs. Alkaline solutions may hydrolyse doxorubicin. Doxorubicin should not be mixed with heparin or 5-fluorouracil. Contact with aluminum should be avoided.

6.3 Shelf Life

Following the special precautions for storage (see below) the shelf life for the powder for solution for injection is 5 years. The expiration date is printed on the label.

Chemical and physical in-use stability of the reconstituted solution in 0.9% sodium chloride solution has been demonstrated for 7 days at 15-25°C and for 14 days under refrigeration (2-8°C).

Chemical and physical in-use stability of a 0.5mg/ml solution in water for injections has been demonstrated for 24 hours at temperatures below 25°C.

Chemical and physical in-use stability of solutions in the range 0.05mg/ml to 5mg/ml in 0.9% sodium chloride solution has been demonstrated for 7 days at room temperature (15-25°C).

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 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special Precautions for Storage

Doxorubin, powder for solution for injection, should be stored at 15-25°C, protected from light.

6.5 Nature and Contents of Container

Doxorubin, powder for solution for injection, 50 mg is supplied as a red-orange, sterile, lyophilised powder, in glass injection vials with aluminium seal. The package size is 1 or 10 vials.

6.6 Instruction for Use, Handling and Disposal

Instructions for reconstitution:

For intravenous injection, Doxorubicin powder for solution for injection should be reconstituted to a concentration of 2 mg/ml in water for injections immediately before use. Alternatively, sodium chloride for injections may be used as a solvent, however, the product may take longer to dissolve.

In order to reconstitute the product, ensure the powder, solutions and equipment are at room temperature, add 25 ml to the 50 mg vial and shake for at least 60 seconds and leave to stand at room temperature for at least 5 minutes before administration to get a clear red mobile liquid. If gelatinous fragments are seen, leave the solution to stand for 5 minutes and shake again. Should the fragments still be visible, discard the solution.

When water for injections is used, immediate dilution to a concentration of less than 0.4 mg/ml doxorubicin with 0.9% sodium chloride solution or 5% glucose solution is needed in order to obtain an isotonic solution.

Due to the toxic nature of doxorubicin it is recommended that the following protective measures be taken:

General instructions for safe use of cytotoxics:

- Training in good techniques for reconstitution and handling should be given to relevant personnel.
- Pregnant staff should be excluded from working with this drug
- Protective clothing should be worn while administering, handling or reconstituting doxorubicin
- Contact with skin or eyes should be avoided. If it occurs, the affected area should be washed immediately with water, soap and water or sodium bicarbonate solution.
- Any spillages should be cleaned with dilute sodium hypochlorite solution.
- All equipment used for the handling, preparation and administration of doxorubicin should be incinerated.
- Unused products should be disposed of in a suitable labelled container, marked as hazardous waste.

7. MARKETING AUTHORISATION HOLDER

Pharmachemie B.V.
Swensweg 5
PO Box 552
2003 RN Haarlem
The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

PL 04946/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

12 July 1993

10. DATE OF (PARTIAL) REVISION OF THE TEXT

April 2005