

Product Name:

- **DOXRED**
10 mg/5 ml
- **DOXRED**
50 mg/25 ml

Dosage form and strength:

- Each 5,0 ml solution contains 10,0 mg
Doxorubicin Hydrochloride
- Each 25,0 ml solution contains 50,0 mg
Doxorubicin Hydrochloride

Amendment date: 15 February 2022

PACKAGE INSERT

Scheduling status: **S4**

Proprietary names and dosage forms:

DOXRED 10 mg/5 ml solution for infusion

DOXRED 50 mg/25 ml solution for infusion

Composition:

DOXRED 10 mg/5 ml solution for infusion: contains 2 mg of doxorubicin hydrochloride per 1 ml of solution.

DOXRED 50 mg/25 ml solution for infusion: contains 2 mg of doxorubicin hydrochloride per 1 ml of solution.

Pharmacological classification:

A 26 Cytostatic agents

Pharmacological action:

A number of important biochemical effects have been described for doxorubicin, an anthracycline antibiotic, any one or all of which could have a role in its therapeutic and toxic effects. The best documented mechanism is its ability to interact with DNA, presumably by intercalation of the planar aglycon moiety between two adjacent base pairs. Another mechanism of action may be binding to cell membranes, resulting in altered permeability properties.

A third mechanism involves the formation of free radicals. There is evidence that free-radical formation may have a role in mutagenicity and cardiotoxicity of doxorubicin.

Indications:

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DOXRED may be included in combination regimens for the treatment of disseminated neoplastic conditions, such as acute leukaemia, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, lymphoma of Hodgkin and non-Hodgkin type, small cell lung cancer, gastric carcinoma and bladder carcinoma.

Contra-indications:

Pre-existing heart disease.

Marked myelosuppression induced by previous chemotherapy or radiotherapy.

Previous treatment with complete cumulative doses of doxorubicin or other anthracyclines.

Pregnancy and lactation:

DOXRED is a potentially embryotoxic and teratogenic agent. The benefits to the pregnant patient should therefore be carefully weighed against the potential toxicity to the embryo and foetus.

DOXRED is excreted into breast milk in small amounts. As far as possible, usage during pregnancy and lactation should be avoided.

Warnings:

Acute life threatening arrhythmias may occur during or within a few hours after DOXRED administration.

DOXRED should not be mixed with 5-fluorouracil, aminophylline or heparin. It is not recommended that doxorubicin be mixed with other medication.

DOXRED should be used only in life-threatening situations. Doses should not be repeated in patients with bone-marrow depression or with mouth ulcers.

Dosage and directions for use:

The most commonly used dosage schedule is 60 – 75 mg/m² as a single intravenous injection administered at 21 day intervals. Lower doses may be required in patients with inadequate marrow reserves. An alternative dosage schedule is 20 mg/m² weekly.

DOXRED dosage should be reduced if the bilirubin is elevated as follows:

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serum bilirubin 21 – 51 $\mu\text{mol/l}$ – give $\frac{1}{2}$ the normal dose

serum bilirubin greater than 51 $\mu\text{mol/l}$ – give $\frac{1}{4}$ the normal dose

Vascular – phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

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

Side-effects and special precautions:

Close observation of the patient and extensive laboratory monitoring is required on initial treatment with doxorubicin. It is recommended, therefore, that patients be hospitalised at least during the first phase of the treatment. In patients using doxorubicin, abnormal liver function tests may occur.

Dose limiting toxicities of therapy are cardiotoxicity and myelosuppression.

Other adverse reactions reported are:

Gastrointestinal:

Nausea, vomiting and abdominal pain, occur frequently and may be severe.

Mucositis (stomatitis and oesophagitis) may occur 5 to 10 days after administration. The effect may be severe resulting in ulceration and represents a site of origin for severe infections. The greater incidence and severity of mucositis is a result of the dose regimen, consisting of administration of doxorubicin on three consecutive days. Ulcerations and necrosis of the colon, especially caecum may occur leading to bleeding or severe infections which can be fatal. Diarrhoea and anorexia have been reported.

Cutaneous:

In most cases, reversible and complete alopecia occurs. Hyperpigmentation of nail -beds and dermal creases, primarily in children, and onycholysis have been reported. Recurrence of skin reaction due to prior radiotherapy has occurred with doxorubicin administration.

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Amendment date: 15 February 2022***Local:***

DOXRED is very irritant and thrombophlebitis and erythematous streaking of the skin over the vein used for injection has been reported; extravasation is serious and may produce extensive local tissue necrosis, ulceration, severe cellulitis and vesicle formation.

Hypersensitivity:

Chills, fever, urticaria, and pruritus have been reported. Anaphylaxis may occur. A case of apparent cross-sensitivity to lincomycin has been reported.

Other:

Facial flushing, conjunctivitis and lacrimation may occur. Malaise, weakness, pulmonary fibrosis, central and peripheral neurotoxicity, headache, hypotension and gynaecomastia may occur.

Special attention must be given to the cardiac toxicity exhibited by doxorubicin.

Acute left ventricular failure has occurred, particularly in patients who have received total dosage exceeding the currently recommended limit of 550 mg/m².

In patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide, the limit appears to be lower.

Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of doxorubicin therapy. Cardiac failure is often not favourably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of heart failure is important. Severe cardiac toxicity may occur precipitously without antecedent electrocardiogram (ECG) changes. A baseline ECG and ECGs should be performed prior to each dose. ECG changes consisting of T₀ -wave flattening, S -T depression and arrhythmias lasting up to two weeks after a dose or course of doxorubicin may occur.

DOXRED cardiomyopathy may be associated with a persistent reduction in the voltage of the QRS wave, a prolongation of the systolic time interval and a reduction of the ejection fraction as determined by echocardiography or radionuclide angiography. The benefit of continued therapy must be carefully evaluated

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against the risk of producing irreversible cardiac damage if test results indicate change in cardiac function associated with DOXRED.

There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematologic monitoring. Leucopenia is reversible and reaches its nadir at 10 to 14 days after treatment. During treatment, white blood cell counts as low as 1000 mm are to be expected. Red blood cells and platelet levels should also be monitored since they may also be depressed. Haematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in super-infection or haemorrhage.

DOXRED has mutagenic and immunosuppressant effects which may stimulate the development of neoplasms after prolonged use.

Evaluation of hepatic function is recommended prior to the individual dosing as toxicity is enhanced by hepatic impairment.

Necrotizing colitis manifested by typhilitis (caecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of doxorubicin and cytarabine.

Doxorubicin must be used carefully in debilitated patients and the elderly and the dose should be reduced in these patients.

On intravenous administration of doxorubicin, extravasion may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred the injection or infusion should be immediately terminated and re-started in another vein.

The area of injection should be frequently examined and plastic surgery consultation obtained because of the progressive nature of extravasation reactions.

Early wide excision of the involved area should be considered. Doxorubicin should not be injected intramuscularly or subcutaneously.

DOXRED may induce hyperuricaemia secondary to rapid lysis of neoplastic cells and uric acid nephropathy may occur. Blood uric acid levels should therefore be monitored. DOXRED may also cause hyperphosphataemia.

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DOXRED imparts a red colouration to the urine 1 to 2 days after administration.

The occurrence of secondary acute myeloid leukaemia with or without a preleukaemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1 to 3 years) latency period.

Interactions:

Radiation - induced toxicity to the myocardium, mucosae, skin and liver has been reported to be increased by the administration of doxorubicin.

The toxicity of other anticancer therapies may be potentiated by doxorubicin. Exacerbation of cyclophosphamide-induced cystitis and enhancement of 6-mercaptopurine hepatotoxicity have been reported.

Known symptoms of overdose and particulars of its treatment:

The toxic effects of mucositis, leucopenia and thrombocytopenia are enhanced by the acute overdose of doxorubicin. Treatment of acute overdose consists of treatment of the severely myelosuppressed patient with hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis. Chronic overdose with cumulative doses exceeding 550 mg/ m² increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of the congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

Identification:

DOXRED 10 mg/5 ml solution for infusion:	Clear, blood-red solution, free of particles
DOXRED 50 mg/25 ml solution for infusion:	Clear, blood-red solution, free of particles

Presentation:

DOXRED 10 mg/5 ml solution for infusion:	A clear, blood-red solution, free of particles filled into a 5 ml amber glass vial and sealed with a
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grey rubber stopper, fluoropolymer coated on
the lower part.

DOXRED 50 mg/25 ml solution for infusion:

Clear, blood-red solution, free of particles filled
into a 25 ml amber glass vial and sealed with a
grey rubber stopper, fluoropolymer coated on
the lower part.

Storage instructions:

Refrigerate at 2 to 8 °C. Protect from light. Do not freeze.

Keep in outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

Registration numbers:

DOXRED 10 mg/5 ml solution for infusion: 37/26/0030

DOXRED 50 mg/25 ml solution for infusion: 37/26/0031

Name and business address of applicant:

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