120 mm

120 mm

270 mm

1110842 DS831

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

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:
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/m^2 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/m^2 weekly.
DOXRED dosage should be reduced if the bilirubin is elevated as follows:
serum bilirubin 21 – 51 μmol/l – give ½ the normal dose
serum bilirubin greater than 51 μmol/l – give ¼ 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.

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/m^2.
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.

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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 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^3 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 typhlitis (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.
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 overdosage and particulars of its treatment:
The toxic effects of mucositis, leucopenia and thrombocytopenia are enhanced by the acute overdosage of doxorubicin. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.
Chronic overdosage with cumulative doses exceeding 550 mg/ m^2 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 10 ml amber glass vial and sealed with a 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 50 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:
Oethmaan Biosims (Pty) Ltd
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Date of publication of this package insert:
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Naprod Packaging Development:

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Prepared by Artcell Dept.	Checked by PD Dept.	Reviewed & Approved by QA Dept.

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1110842 DS831

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

Skeduleringstatus: S4

Eiendomsnaam en doseervorms:
DOXRED 10 mg/5 ml oplossing vir infusie
DOXRED 50 mg/25 ml oplossing vir infusie

Samestelling:
Elke DOXRED 10 mg/5 ml oplossing vir infusie bevat 2 mg doksorubisienhidrochloried per 1 ml oplossing.
Elke DOXRED 50 mg/25 ml oplossing vir infusie bevat 2 mg doksorubisienhidrochloried per 1 ml oplossing.

Farmakologiese klassifikasie:
A 26 Sitostatiese middels

Farmakologiese werking:
'n Aantal belangrike biologiese effekte word aan doksorubisien, 'n antrasiklienantibiotikum, toegeskryf waarvan enigeen of almal 'n rol in die terapeutiese en toksiese effekte daarvan kan speel. Die meganisme wat die beste gedokumenteer is, is die vermoë daarvan om met DNA te interageer, waarskynlik deur interkalasie van die planêre aglukoon tussen twee naasliggende basispare. Nog 'n werkingsmeganisme kan binding aan selmembrane wees wat tot verandering in deurlaatbaarheid lei.
'n Derde meganisme behels die vorming van vry radikale. Daar is getuienis dat die vorming van vry radikale 'n rol in die mutagenisiteit en kardiotoksisiteit van doksorubisien kan speel.

Indikasies:
DOXRED kan ingesluit word in kombinasieregimens vir die behandeling van verspreide neoplastiese toestande soos akute leukemie, sarkomas van die sagte weefsel en skeletbene, borskanker, ovariumkanker, Hodgkinse en nie-Hodgkinse limfoom, kleinsellongkanker, maagkanker en blaaskanker.

Kontra-indikasies:
Bestaande hartsiekte.
Merkbare beenmurgonderdrukking geïnduseer deur vorige chemoterapie of radioterapie.
Vorige behandeling met volledige kumulatiewe dosisse doksorubisien of ander antrasikliene.

Swangerskap en borsvoeding
DOXRED is 'n middel wat moontlik embriotoksies en teratogenies is. Die voordele vir die swanger pasiënt moet daarom noukeurig teen die moontlike toksisiteit vir die embrio en die fetus opgeweeg word.
DOXRED word in klein hoeveelhede in borsmelk uitgeskei. Gebruik tydens swangerskap en borsvoeding moet sover as moontlik vermy word.

Waarskuwings
Akute lewensbedreigende aritmie kan tydens of binne die eerste paar uur na toediening van DOXRED voorkom.
DOXRED moet nie met 5-fluoorurasiel, aminofillien of heparien gemeng word nie. Dit word nie aanbeveel dat doksorubisien met enige ander medikasie gemeng word nie.
DOXRED moet slegs in lewensbedreigende situasies gebruik word. Vir pasiënte met beenmurgonderdrukking of ulkusse in die mond moet dosering nie herhaal word nie.

Dosis en gebruiksaanwysings:
Die mees algemeen gebruikte dosis is 60 – 75 mg/m^2 as 'n enkele intraveneuse inspuiting met intervalle van 21 dae toegedien. Laer dosisse kan nodig wees vir pasiënte met onvoldoende beenmurgreserwes. 'n Alternatiewe doseerskedule is 20 mg/m^2 weekliks.
Die dosis van DOXRED moet as volg verminder word as die bilirubienvlakke styg:
21 – 51 μmol/l bilirubien in die serum – gee ½ van die normale dosis
meer as 51 μmol/l bilirubien in die serum – gee ¼ van die normale dosis
Vaskulêre flebosklerose is aangemeld veral as klein are gebruik word of as 'n enkele aar vir herhaaldelike toediening gebruik word. Blosing in die gesig kan voorkom as die inspuiting te vinnig gegee word.
Die totale dosis doksorubisien wat aan 'n individuele pasiënt toegedien word, moet vorige of gelyktydige behandeling met verwante verbindings, soos daunorubisien, in ag neem.

Newe-effekte en spesiale voorsorgmaatreëls:
Noukeurige observasie van die pasiënt en uitgebreide laboratoriumtoetse is tydnes aanvanklike behandeling met doksorubisien nodig. Dit word dus aanbeveel dat pasiënte vir ten minste die eerste fase van behandeling in die hospitaal opgeneem word. Abnormale lewerfunksie kan voorkom in pasiënte wat doksorubisien gebruik.
Kardiotoksisiteit en beenmurgonderdrukking is effekte wat die dosis van behandeling beperk.

Ander nadelige reaksies wat aangemeld is, is die volgende:

Gastro-intestinaal:
Naarheid, braking en buikpyn, kom dikwels voor en kan erg wees.
Mukositis (stomatitis en esofagitis) kan 5 – 10 dae na toediening voorkom. Die effek kan ernstig wees en kan ulkusse veroorsaak wat oorsprong aan ernstige infeksies kan gee. Toediening van doksorubisien op drie opeenvolgende dae kan tot 'n hoër voorkoms en erger graad van mukositis lei. Ulserasie en nekrose van die kolon, en veral die sekum, kan voorkom wat kan lei tot bloeding of erge infeksies wat dodelik kan wees. Diarree en anoreksie is aangemeld.

Vel:
In die meeste gevalle kom omkeerbare en volledige alopesie voor. Hiperpigmentasie van die naelbed en velvoue, veral in kinders, asook omigolise is aangemeld. Terugkeer van velreaksies vanweë vorige radioterapie het na toediening van doksorubisien voorgekom.

Plaaslik:
DOXRED is baie irriterend en tromboflebitis en eriteemagtige strepe van die vel oor die aar wat vir inspuiting gebruik word, is aangemeld; ekstravasasie is ernstig en kan uitgebreide plaaslike weefselnekrose, ulserasie, ernge sellulitis en vesikelvorming veroorsaak.

Hipersensitiwiteit:
Kouekoors, koors, urtikarie en pruritus is aangemeld. Anafilakse kan voorkom. 'n Geval van blykbare kruissensitiwiteit met linkomisien is aangemeld.

Ander:
Blosing in die gesig, konjuntivitis en lakrimasie kan voorkom. Ongesteldheid, swakheid, pulmonêre fibrose, sentrale en perifere neurotoksisiteit, hoofpyn, hipotensie en ginekomastie kan voorkom.
Spesiale aandag moet gegee word aan die kardiotoksisiteit van doksorubisien.
Akute linkerventrikulêre versaking het voorgekom veral in pasiënte wat 'n totale dosis ontvang het wat die huidige aanbevole limiet van 550 mg/m^2 oorskry.
Dit lyk asof die limiet laer is in pasiënte wat radioterapie van die mediastinale gebied of gelyktydige behandeling ontvang met ander middels wat moontlik kardiotoksies is, soos siklofosfamied.
Kongestiewe hartversaking en/of kardiomiopatie kan

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etlike weke na staking van behandeling met doksorubisien voorkom. Hartversaking reageer dikwels nie gunstig op huidige bekende mediese of fisiese behandeling ter ondersteuning van hartfunksie nie. Vroeë diagnose van hartversaking is belangrik. Ernstige kardiotoksisiteit kan skielik sonder enige vooraf veranderings in die elektrokardiogram (EKG) voorkom. 'n Basislyn-EKG moet gedoen word asook EKG's voor elke dosis. Veranderings in die EKG kan voorkom, soos 'n afplatting van die T0-golf, onderdrukking van S-T-sein en aritmie wat vir tot twee weke na 'n dosis of kursus van doksorubisien kan duur.
Kardiomiopatie vanweë DOXRED kan gepaardgaan met 'n volgehoue afname in die spanning van die QRS-golf, 'n verlenging in die sistoliese interval en 'n afname in die uitsetfraksie soos bepaal met eggokardiografie of radionukliedangiografie. Die voordeel van voortgesette behandeling moet noukeurig opgeweeg word teen die risiko vir onomkeerbare hartskade as die toetsresultate 'n verandering in hartfunksie vanweë DOXRED aantoon.
Daar is hoë voorkoms van beenmurgonderdrukking, veral van leukosiete, en noukeurige monitering van hematologiese funksie is nodig. Leukopenie is omkeerbaar en bereik sy trog 10 tot 14 dae na behandeling. Tellings van witbloedselle so laag as 1000/mm^3 kan tydens behandeling verwag word. Die vlakke van rooibloedselle en plaatjies moet ook gemonitor word omdat hulle ook laer kan wees. 'n Verlaging in die dosis of opskorting of uitstel van behandeling met doksorubisien kan vanweë hematologiese toksisiteit nodig wees. Volgehoue erge beenmurgonderdrukking kan tot superinfeksie of bloeding lei.
DOXRED het mutageniese en immuunonderdrukkende effekte wat na langdurige gebruik die ontwikkeling van neoplasmas kan stimuleer.
Beoordeling van lewerfunksie word voor dosering van elke individu aanbeveel omdat toksisiteit deur swak lewerfunksie versterk word.
Nekrotiese kolitis waargeneem as tiflitis (inflammasie van die sekum), bloederige stoelgang en ernstige en soms dodelike infeksies het voorgekom met die kombinasie van doksorubisien en sitarabien.
Doksorubisien moet versigtig gebruik word in verswakte en bejaarde pasiënte en die dosis vir hierdie pasiënte moet verlaag word.
Tydens intraveneuse toediening van doksorubisien kan ekstravasasie met of sonder 'n gepaardgaande brand- of steekgevoel voorkom selfs as die bloed met aspirasie goed in die infusienaald optrek. As tekens of simptome van ekstravasasie voorkom, moet die inspuiting of infusie onmiddellik gestaak en van nuuts af in 'n ander aar gegee word.
Die omgewing rondom die inspuiting moet gereeld ondersoek word en die advies van 'n plastiese chirurg moet verkry word vanweë die progressiewe aard van reaksies tydens ekstravasasie.
'n Vroeë en wye eksisie van die betrokke area moet oorweeg word. Doksorubisien moet nie intramuskulêr of subkutaan ingespuit word nie.
DOXRED kan hiperurisemie vanweë vinnige lise van neuplastiese selle veroorsaak en uriensuurnefropatie kan voorkom. Die vlakke van uriensuur in die bloed moet daarom gemonitor word. DOXRED kan ook hiperfosfatemie veroorsaak.
DOXRED veroorsaak 'n rooi verkleuring van die urien vir 1 tot 2 dae na toediening.
Die voorkoms van sekondêre akute miëloïedleukemie met of sonder 'n preleukemiese fase is in enkele pasiënte aangemeld wat terselfdertyd behandel is met doksorubisien en 'n antineoplastiese middel wat DNA-skade veroorsaak. Sulke gevalle kan 'n kort (1 tot 3 jaar) sluimerende periode hê.

Interaksies
Dit is gemeld dat toksisiteit van die miokardium, slymvliese, vel en lewer vanweë bestraling deur die toediening van doksorubisien vererger word.
Die toksisiteit van ander antikankermiddels kan deur doksorubisien versterk word. 'n Verergering van sistitis vanweë siklofasfamied en versterking van hepatoksisiteit deur 6-merkaptopurien is aangemeld.

Bekende simptome van oordosering en besonderhede vir die behandeling daarvan
Die toksiese effekte soos mikositis, leukopenie en trombositopenie word deur akute oordosering met doksorubisien versterk. Behandeling van akute oordosering behels die behandeling van die pasiënt met ernstige beenmurgonderdrukking deur hospitalisasie, antibiotika, oortapping van plaatjies en granulosiete en simptomatiese behandeling van mikositis.
Chroniese oordosering met kumulatiewe dosisse groter as 550 mg/m^2 verhoog die risiko vir kardiomiopatie en gevolglike kongestiewe hartversaking. Behandeling bestaan uit drastiese beheer van die kongestiewe hartversaking met digitalis en diuretika. Die gebruik van perifere vasodilatore word aanbeveel.

Identifikasie
DOXRED 10mg/5ml oplossing vir infusie: Helder, bloedrooi oplossing vry van deeltjies
DOXRED 50mg/25ml oplossing vir infusie: Helder, bloedrooi oplossing vry van deeltjies

Aanbieding
DOXRED 10 mg/5 ml oplossing vir infusie: 'n Helder, bloedrooi oplossing vry van deeltjies in 'n bruin glasflessie van 10 ml verseël met 'n grys rubberprop wat aan die onderkant met 'n fluoorpolimeer bedek is.
DOXRED 50 mg/25 ml oplossing vir infusie: 'n Helder, bloedrooi oplossing vry van deeltjies in 'n bruin glasflessie van 50 ml verseël met 'n grys rubberprop wat aan die onderkant met 'n fluoorpolimeer bedek is.

Bewaringsinstruksies:
Hou verkoel by 2 - 8 °C. Beskerm teen lig. Moenie vries nie.
Hou in die karton totdat dit benodig word.
HOU BUITE DIE BEREIK VAN KINDERS.

Registrasienommers:
DOXRED 10 mg/5 ml oplossing vir infusie:
37/26/0030
DOXRED 50 mg/25 ml oplossing vir infusie:
37/26/0031

Naam en besigheidsadres van applikant:
Oethmaan Biosims (Edms) Bpk
Kantoor 207A, 1ste verdieping, Sherwood House
Greenacres Office Park, H/v Victory- & Rustenburgweg
Victory Park, 2195
Johannesburg, RSA

Datum van publikasie van hierdie voubiljet
Junie 2003

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Doxred DS (South Africa)
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Naprod Packaging Development:

Artwork prepared by: Avani Sawant	**PP No.:** INJ00XXXX
Artwork Approval Date:	**PP Date:** XX/XX/XXXX

Prepared by Artcell Dept.	Checked by PD Dept.	Reviewed & Approved by QA Dept.

Digitally signed by Shahaboodeen
DN: cn=Shahaboodeen, o=Oethmaan Biosims (Pty) Ltd, ou=Regulatory Affairs, email=regulatory@oethmaan.co.za, c=ZA
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