PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. **NAME OF THE MEDICINE:**

DOXRED LYO 10 (Powder for solution for infusion)

DOXRED LYO 50 (Powder for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

DOXRED LYO 10: Each 5 ml vial contains doxorubicin hydrochloride 10 mg.

Contains sugar (lactose monohydrate 50 mg/vial).

DOXRED LYO 50: Each 25 ml vial contains doxorubicin hydrochloride 50 mg.

Contains sugar (lactose monohydrate 250 mg/vial).

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

A red coloured lyophilized mass.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

DOXRED LYO is indicated for the treatment of:

- Acute leukaemias (acute lymphoblastic leukaemia [ALL] and acute myelogenous leukaemia [AML]), lymphomas and a number of solid tumours.
- Metastatic adenocarcinoma of the breast, carcinoma of the bladder, bronchogenic carcinoma and neuroblastoma.

- Metastatic thyroid carcinoma, carcinoma of the endometrium, testes, prostate, cervix, head and neck, and plasma cell myeloma.
- Carcinoma of the ovary against which it is active when administered with cisplatin and cyclophosphamide.
- Carcinoma of the breast and small (oat) cell carcinoma of the lung when administered concurrently with other cytotoxic medicines.
- A wide range of sarcomas including osteogenic, Ewing's and soft tissue sarcoma.
- Hodgkin's disease where it is effective in the ABVD (doxorubicin / bleomycin / vinblastine / dacarbazine) combination.
- Non-Hodgkin's lymphomas if administered concurrently in the BACOP combination.

4.2 Posology and method of administration

Posology

Treatment of solid tumours:
When **DOXRED LYO** is administered as a single agent, the recommended dose per cycle is 60 – 90 mg/m^2 of body surface area every 3 – 4 weeks. Administration of **DOXRED LYO** in a weekly regimen of 10 – 20 mg/m^2 has also been shown to be effective. The medicine is generally given as a single dose per cycle; however, it is possible to give the dosage per cycle in divided administrations:

- 0,6 mg/kg/day for 3 days (25 mg/m^2/day for 3 days), or
- 0,8 mg/kg/day for 2 days (30 mg/m^2/day for 2 days), or
- 1,6 mg/kg/day for 1 day (60 mg/m^2/day for 1 day).

If **DOXRED LYO** is used in combination with other antitumour agents, the recommended dose per cycle is in the 30 – 60 mg/m^2 range, repeated every 21 days. As **DOXRED LYO** is a myelosuppressive agent, the interval between cycles may need to be increased, or the dosage reduced, in patients whose WBC counts (particularly neutrophils) are below the

range of normal values before any treatment cycle. Dosage may also need to be reduced in children, in the elderly, obese patients and in pretreated patients in whom the marrow reserve may be low.

Treatment of acute leukaemias:

In acute leukaemia the dosage schedule is based on the patient's response.

0,4 – 0,5 mg/kg/day for 3 days is the recommended starting dose. According to the antileukaemia and myelosuppressive effect obtained, this course can be repeated a second or even a third time with an interval between courses of not less than 7 – 10 days.

Special populations:

Hepatic dysfunction:

In the presence of impaired hepatic function, it is suggested that **DOXRED LYO** dosage be reduced as follows:

Serum Bilirubin	Dose Reduction
1,2 – 3,0 mg / 100 ml	50 % (i.e. 50 % of normal dose to be given
> 3 mg / 100 ml	75 % (i.e. 25 % of normal dose to be given)

DOXRED LYO should not be administered to patients with severe hepatic impairment (see section 4.3).

Method of administration

DOXRED LYO is administered by intravenous injection only. It should not be given orally and should not be injected intramuscularly or subcutaneously.

Intravenous administration:

Intravenous administration of **DOXRED LYO** should be performed with caution. It is recommended that **DOXRED LYO** be administered into the tubing of a freely flowing intravenous infusion (isotonic sodium chloride or 5 % glucose solution) over a period of 3 to 5 minutes. This technique is intended to minimise the risk of thrombosis or perivenous extravasation.

Any unused portion must be discarded as this preparation is intended for single dose administration.

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 (see section 4.4).

For instructions on reconstitution of the **DOXRED LYO** before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to doxorubicin or any of the excipients listed in section 6.1, other anthracyclines or anthracenediones.
- Persistent myelosuppression.
- Hepatic impairment.
- Myocardial insufficiency.
- Recent myocardial infarction.
- Severe dysrhythmias.
- Previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (see section 4.4).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

DOXRED LYO should be administered only under the supervision of a doctor experienced in cancer chemotherapy.

Patients should be advised not to conceive and the use of reliable contraceptives is advised (see section 4.3 and section 4.6).

Initial treatment calls for a careful baseline monitoring of various laboratory parameters and cardiac function. Blood counts and measurement of haemoglobin concentration should be carried out routinely.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia and generalised infections) before beginning treatment with **DOXRED LYO**.

DOXRED LYO is incompatible with heparin and should also not be mixed with other medicines.

DOXRED LYO should be given with great care, in reduced doses, to elderly patients and to those with hepatic impairment.

The systemic clearance of doxorubicin is reduced in obese patients (i.e. > 130 % ideal body weight) (see section 4.2).

Cardiac function:

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early events: This consists mainly of sinus tachycardia and/or ECG abnormalities, such as non-specific ST-T wave changes. Tachydysrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia as well as atrioventricular and bundle-branch block have also been reported. These events do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for discontinuation of **DOXRED LYO** treatment.

Late events: Delayed cardiotoxicity usually develops late in the course of therapy with **DOXRED LYO** or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF), such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. Subacute effects, such as pericarditis/myocarditis, have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the medicine.

Cardiac function should be assessed before patients undergo treatment with **DOXRED LYO** and must be monitored throughout therapy to minimise the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of **DOXRED LYO** at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluations of LVEF) includes multi-gated radionuclide angiography or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a multi-gated radionuclide angiography scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated multi-gated radionuclide angiography or

ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses.

To reduce the effects of cardiotoxicity the total cumulative dose of doxorubicin should not exceed 500 mg/m^2 body surface area.

Haematological toxicity:

DOXRED LYO may produce myelosuppression. Haematological profiles should be assessed before and during each cycle of therapy with **DOXRED LYO**, including differential white blood cell (WBC) counts. A dose- dependent, reversible leukaemia and/or granulocytopenia (neutropenia) is the predominant manifestation of **DOXRED LYO** haematological toxicity and is the most common acute dose-limiting toxicity of this medicine. Leukopenia and neutropenia generally reach the nadir between days 10 – 14 after medicine administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Secondary leukaemia:

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

Carcinogenesis, Mutagenesis and Fertility impairment:

Doxorubicin was genotoxic and mutagenic *in vitro* and *in vivo* tests.

In women, **DOXRED LYO** may cause infertility during the time of medicine administration. **DOXRED LYO** may cause amenorrhoea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

DOXRED LYO is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent. Men undergoing **DOXRED LYO** treatment should use effective contraceptive methods.

Gastrointestinal:

DOXRED LYO is emetogenic. Mucositis/stomatitis generally appears early after medicine administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Liver function:

The major route of elimination of **DOXRED LYO** is the hepatobiliary system. Serum total bilirubin should be monitored before and during treatment with **DOXRED LYO**. Patients with elevated bilirubin may experience slower clearance of the medicine with an increase in overall toxicity. Lower doses are recommended in these patients (see section 4.2). Patients with severe hepatic impairment should not receive **DOXRED LYO** (see section 4.3).

Effects at site of injection:

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2).

Extravasation:

Extravasation of **DOXRED LYO** during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of **DOXRED LYO**, the medicine infusion should be stopped immediately.

Other

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported. Radiation-induced toxicities (myocardium, mucosae, skin and liver) have also been reported.

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of doxorubicin.

Tumour-Lysis Syndrome

Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumour-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumour lysis syndrome.

Vaccinations

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections.

Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Excipient Information

DOXRED LYO contains lactose monohydrate. Patients with hereditary galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should therefore not receive **DOXRED LYO**.

After reconstitution, DOXRED LYO 10 and DOXRED LYO 50 contain 17,7 mg and 88,5 mg sodium per vial, equivalent to 0,9 % and 4,43 % of the WHO maximum daily intake (RDI) of 2 g sodium for and adult, respectively.

4.5 Interaction with other medicinal products and other forms of interaction

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g, verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (e.g, phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin.

The addition of ciclosporin to doxorubicin may result in increases in area under the concentration-time curve (AUC) for both doxorubicin and doxorubicinol, possibly due to a decrease in clearance of the parent compound and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding ciclosporin to doxorubicin results in more profound and prolonged haematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of ciclosporin and doxorubicin.

High dose ciclosporin increases the serum levels and myelotoxicity of doxorubicin.

DOXRED LYO is mainly used in combination with other cytotoxic medicines. Additive toxicity may occur especially with regard to bone marrow/haematological and gastrointestinal effects (see section 4.4). The use of **DOXRED LYO** in combination chemotherapy with other potentially cardiotoxic medicines, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment. Changes in hepatic function induced by concomitant therapies may affect **DOXRED LYO** metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

Paclitaxel can cause increased plasma-concentrations of doxorubicin and/or its metabolites when given prior to doxorubicin. Certain data indicate that a smaller increase is observed when doxorubicin is administered prior to paclitaxel.

The use of trastuzumab in combination with anthracyclines (such as doxorubicin hydrochloride) is associated with an increased cardiotoxic risk. Trastuzumab and anthracyclines should currently not be used in combination, except for well controlled clinical studies with monitoring of cardiac function (see section 4.4).

In a clinical study, an increase in doxorubicin AUC of 21 % was observed when given with sorafenib 400 mg twice daily. The clinical significance of this finding is unknown.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential, male/female contraception

Women of childbearing potential have to use effective contraception during treatment (see section 4.4).

Men undergoing **DOXRED LYO** treatment should use effective contraceptive methods. (see section 4.4).

The use of **DOXRED LYO** is contra-indicated during pregnancy and lactation as safety and efficacy have not been established (see section 4.3 and 4.4).

Pregnancy:

Doxorubicin has harmful pharmacological effects on pregnancy and/or the foetus/newborn child. Due to the embryotoxic potential of doxorubicin, **DOXRED LYO** should not be used during pregnancy. If a woman receives doxorubicin during pregnancy or becomes pregnant whilst taking **DOXRED LYO**, she should be warned of the potential hazard to the foetus.

Breastfeeding:

Doxorubicin is secreted into breast milk. Women should not breastfeed while undergoing treatment with doxorubicin.

Fertility:

See section 4.4

4.7 Effects on ability to drive and use machines

DOXRED LYO has no or negligible effects on the ability to drive or use machinery.

4.8 Undesirable effects

The following adverse events have been reported in association with **DOXRED LYO** therapy:

System Organ Class	**Adverse reaction**	**Frequency**
Infections and infestations	Infection, sepsis/septicaemia.	Frequent
Neoplasms Benign,	Acute lymphocytic leukaemia, Acute	Frequency

Malignant and Unspecified (including cysts and polyps)	myeloid leukaemia	unknown
Blood and lymphatic system disorders	Leukopenia (see section 4.4), anaemia, thrombocytopenia, haemorrhage, and neutropenia.	Frequent
Immune system disorders	Anaphylaxis, allergic reaction	Less frequent
Metabolism and nutrition disorders	Hyperuricaemia or uric acid nephropathy. This occurs most commonly during initial treatment of patients with leukaemia or lymphoma as a result of rapid cell breakdown that leads to elevated serum uric acid concentrations.	Less frequent
Eye disorders:	Conjunctivitis/keratitis, lacrimation.	Less frequent
Cardiac disorders	ECG abnormalities, sinus tachycardia, tachydysrhythmias, atrioventricular and bundle branch block, asymptomatic reductions in left ventricular ejection fraction, and congestive heart failure (see section 4.4).	Frequent
Vascular disorders	Phlebitis, thrombophlebitis, thromboembolism, hot flushes	Less frequent
Gastrointestinal disorders	Oesophagitis, stomatitis, nausea and vomiting (may be severe), diarrhoea,	Frequent

	mucositis, abdominal pain, anorexia, and dehydration	
	Gastric erosions, gastrointestinal bleeding, hyperpigmentation of the oral mucosa, colitis, and gastrointestinal ulceration.	Less frequent
Hepatobiliary disorders:	Changes in transaminase levels.	Less frequent
Skin and subcutaneous tissue disorder	Alopecia, rash/itch, skin changes.	Frequent
	Skin and nail hyperpigmentation, hypersensitivity reactions in irradiated skin (radiation recall reactions), photosensitivity urticaria, and acral erythema.	Less frequent
Renal and urinary disorders	Red colouration of urine for 1 to 2 days after administration.	Less frequent
Reproductive system and breast disorders	Amenorrhoea, oligospermia, azoospermia.	Frequent
General disorders and administration site conditions	Malaise/asthenia, fever, chills, shock, local toxicity.	Frequent:
	Extravasation, cellulitis or tissue necrosis at injection site, phlebosclerosis.	Less frequent
Investigation	Ejection fraction decreased, electrocardiogram abnormal, transaminases abnormal, weight	Frequency unknown

	increased	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Medicine Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Acute overdosage would be likely to cause the symptoms listed above, i.e. gastrointestinal symptoms, buccal ulceration and bone marrow depression. Should these symptoms occur, therapy should be stopped. A cumulative dosage above 500 mg/m^2 may cause irreversible cardiac failure. Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A26. Cytostatic agents

ATC Code: L01DB01

Doxorubicin is an antimitotic and cytostatic antibiotic, isolated from cultures of *Streptomyces peucetius var. caesius* with an antineoplastic action. Its exact mechanism of action of antineoplastic activity is unknown, but may involve binding to DNA by intercalatian between base pairs and inhibition of DNA and RNA synthesis by template disordering and obstruction. Other possible mechanisms of antineoplastic activity include binding to cell membrane lipids, thus altering a variety of cellular functions and interacting with topoisomerase II to form DNA-cleavable complexes.

5.2 Pharmacokinetic properties

Distribution:

Doxorubicin is quickly and widely distributed into the extravascular compartments, as indicated by a rapid (5 to 10 min) distribution half-life and by a steady state distribution volume in excess of 20 to 30 litres/kg. However, doxorubicin does not cross the blood- brain barrier in detectable amounts but may cross the placenta and is distributed into breast milk. Binding of doxorubicin to plasma proteins is extensive.

Biotransformation:

Doxorubicin is metabolised to a significant extent by the liver. The major active metabolite is 13-OH-doxorubicinol.

Elimination:

The elimination half-life of doxorubicin and 13-OH-doxorubicinol is 20 to 48 hours. Forty to fifty percent of the administered dose is recovered in the bile or in the faeces in seven days, about half of which is as unchanged compound. Renal excretion is modest, accounting for only 5 – 10 percent of the administered dose in 5 days.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Methyl paraben

Hydrochloric acid

Sodium hydroxide

6.2 Incompatibilities

DOXRED LYO should not be mixed with other medicines. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin.

DOXRED LYO should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

6.3 Shelf life

2 years (proposed)

6.4 Special precautions for storage

Before reconstitution: Store below 30 °C. Protect from light. Keep vial in the outer carton until required for use.

After reconstitution: The reconstituted solution is stable for 7 days at room temperature (below 25 ºC) and under normal room light and 15 days under refrigeration (2 ° to 8 °C). It should be protected from exposure to sunlight. Discard any unused solution.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

DOXRED LYO 10: Carton containing a 5 ml clear, transparent glass vial closed by a grey slotted rubber stopper and 20 mm red flip-off seal.

DOXRED LYO 50: Carton containing a 25 ml clear, transparent glass vial closed by a grey slotted rubber stopper and 20 mm red flip-off seal.

6.6 Special precautions for disposal and other handling

Instructions for use/handling:

Preparation of the freeze-dried powder for intravenous administration:

Dissolve powder in 0,9 % sodium chloride or water for injection to give a final concentration of 2 mg/ml (10 mg/5 ml or 50 mg/25 ml). The vial contents are under negative pressure. To minimise aerosol formation during reconstitution, particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided.

Intravenous administration:

DOXRED LYO should be administered into the tubing of a freely flowing intravenous infusion (0,9 % sodium chloride or 5 % glucose solution) for not less than 3 – 10 minutes to minimise the risk of thrombosis or perivenous extravasation.

Protective measures:

The following protective recommendations are given due to the toxic nature of the substance:

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with **DOXRED LYO**.
- Personnel handling **DOXRED LYO** should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic- backed, absorbent paper.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1 % available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- 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.

- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a medical practitioner.
- Always wash hands after removing gloves.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenburg Roads

Victory Park

Johannesburg

2195

8 REGISTRATION NUMBER(S):

DOXRED LYO 10: 57/26/0698

DOXRED LYO 50: 57/26/0699

9 DATE OF FIRST AUTHORISATION

Date of registration: 20 February 2024

10 DATE OF REVISION OF THE TEXT

Not applicable