PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOXOLIP concentrate for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 mg/1 mL doxorubicin hydrochloride in a pegylated liposomal formulation and delivers 10 mL (20 mg) in a concentrate for infusion for single intravenous use.

Contains sugar: sucrose 100, 00 mg/mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A translucent red coloured liposomal dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

DOXOLIP is indicated as monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.

Ovarian cancer

DOXOLIP is indicated for the treatment of advanced ovarian cancer in women who have failed a first line platinum-based chemotherapy regimen.

Multiple myeloma

DOXOLIP is indicated in combination with bortezomib, for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

AIDS-related Kaposi's sarcoma (KS) DOXOLIP is indicated for AIDS-related Kaposi's sarcoma (KS) in patients with low CD counts (<200 CD lymphocytes per mm^3) and extensive mucocutaneous or visceral disease.

4.2 Posology and method of administration

DOXOLIP is for single use only.

DOXOLIP should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic medicines.

DOXOLIP exhibits unique pharmacokinetic properties and should not be used interchangeably with other formulations of doxorubicin hydrochloride.

Treatment of breast cancer or ovarian cancer

DOXOLIP is administered intravenously at a dose of 50 mg/m^2 once every four weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

Doses < 90 mg: dilute **DOXOLIP** in 250 mL dextrose 5 % in water.

Doses > 90 mg: dilute **DOXOLIP** in 500 mL dextrose 5 % in water.

The initial dose is administered at a rate no greater than 1 mg/minute in order to minimise the risk of infusion reactions.

If no infusion reaction is observed, subsequent **DOXOLIP** infusions may be administered over a 60-minute period.

If an infusion reaction occurs, the method of infusion should be modified as follows: 5 % of the total dose should be infused slowly over the first 15 minutes. If tolerated without a reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

Treatment of multiple myeloma

DOXOLIP is administered at 30 mg/m^2 on day 4 of the bortezomib 3 week regimen as a 1 hour infusion administered immediately after the bortezomib infusion. The bortezomib

regimen consists of 1, 3 mg/m^2 on days 1, 4, 8 and 11, every 3 weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment.

Doses < 90 mg: dilute **DOXOLIP** in 250 mL of 5 % (50 mg/mL) glucose solution for infusion.

Doses ≥ 90 mg: dilute **DOXOLIP** in 500 mL of 5 % (50 mg/mL) glucose solution for infusion.

The intravenous catheter and tubing should be flushed with 5 % glucose solution for infusion between administrations of the 2 medicines. Day 4 dosing of both medicines may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart. The first infusion of **DOXOLIP** should be administered over 90 minutes as follows:

- 10 mL over the first 10 minutes
- 20 mL over the next 10 minutes
- 40 mL over the next 10 minutes
- then complete the infusion over a total of 90 minutes.

Subsequent doses of **DOXOLIP** will be administered over 1 hour, as tolerated. If an infusion reaction to **DOXOLIP** occurs, stop the infusion. After the symptoms have resolved, attempt to administer remaining **DOXOLIP** over 90 minutes as follows:

- 10 mL over the first 10 minutes
- 20 mL over the next 10 minutes
- 40 mL over the next 10 minutes
- then complete the infusion over a total of 90 minutes.

Infusion may be given through a peripheral vein or a central line.

Treatment of AIDS-KS

DOXOLIP should be administered intravenously at 20 mg/m every 2 - 3 weeks. Intervals shorter than 10 days should be avoided as accumulation of the medicine and increased toxicity cannot be ruled out. Patients should be treated for two to three months to achieve a therapeutic response. Treatment should be continued as needed to maintain therapeutic response.

DOXOLIP, diluted in 250 mL dextrose 5 % in water, is administered by intravenous infusion over 30 minutes.

All patients

If the patient experiences early symptoms or signs of infusion reaction, immediately discontinue the infusion, give appropriate pre-medications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

Do not administer as a bolus injection or undiluted solution. It is recommended that the **DOXOLIP** infusion line be connected through the side port of an intravenous infusion of dextrose 5 % in water to achieve further dilution and minimise the risk of thrombosis and extravasations. The infusion may be given through a peripheral vein. **DOXOLIP** must not be given by the intramuscular or subcutaneous route. Do not use with in-line filters.

The dose of **DOXOLIP** may be reduced or delayed in order to manage adverse events such as palmar-plantar erythrodysaesthesia (PPE), stomatitis or haematological toxicity. Guidelines for **DOXOLIP** dose modification secondary to these adverse effects are provided in the tables below.

The tables for PPE (Table 1) and stomatitis (Table 2) provide the schedule followed for dose modification in the treatment of breast or ovarian cancer (modification of the recommended four week treatment cycle). If these toxicities occur in patients with AIDS-related KS, the recommended two to three week treatment cycle can be modified in a similar manner.

Table 3 for haematological toxicity provides the schedule followed for dose modification in the treatment of patients with breast or ovarian cancer. (See section 4.4 for dose modification in patients with AIDS-KS.)

Table 1: Palmar-plantar erythrodysaesthesia

		Week after prior DOXOLIP dose	
Toxicity grade after prior DOXOLIP dose	**Week 4**	**Week 5**	**Week 6**
Grade 1 Mild erythema, swelling, or desquamation not interfering with daily activities.	Redose unless patient has experienced a previous grade 3 or4 skin toxicity, in which case wait an additional week	Redose unless patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week.	Decrease dose by 25 %; return to 4 week interval
Grade 2 Erythema desquamation or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.	Wait an additional week.	Wait an additional week.	Decrease dose by 25 %; return to 4 week interval.
Grade 3 Blistering, ulceration, or swelling interfering with walking or normal daily activities, cannot wear regular clothing	Wait an additional week.	Wait an additional week.	Withdraw patient.

Grade 4 Diffuse or local process causing infectious complications or a bedridden state or hospitalisation	Wait an additional week.	Wait an additional week.	Withdraw patient.

Table 2: Stomatitis

		Week after prior DOXOLIP dose	
Toxicity grade after prior DOXOLIP dose	**Week 4**	**Week 5**	**Week 6**
Grade 1 Painless ulcers, erythema, or mild soreness.	Redose unless patient has experienced a previous grade 3 or 4 stomatitis, in which case wait an additional week.	Redose unless patient has experienced a previous grade 3 or 4 stomatitis, in which case wait an additional week.	Decrease dose by 25 %; return to 4 week interval or withdraw patient per medical practitioner's assessment
Grade 2 Painful erythema, oedema, or ulcers, but can eat.	Wait an additional week.	Wait an additional week.	Decrease dose by 25 %; return to 4 week interval or withdraw patient per medical practitioner's assessment.
Grade 3 Painful erythema, oedema, or ulcers, but cannot eat.	Wait an additional week.	Wait an additional week.	Withdraw patient.

Grade 4 Requires parenteral or enteral support	Wait an additional week.	Wait an additional week.	Withdraw patient.

Table 3: Haematological toxicity (absolute neutrophil count (ANC) or platelets) – management of patients with breast or ovarian cancer only

Grade	ANC	Platelets	Modification
Grade 1	1 500 – 1 900	75 000 – 150 000	Resume treatment with no dose reduction.
Grade 2	1 000 - < 1 500	50 000 - < 75 000	Wait until ANC ≥ 1 500 and platelets ≥ 75 000; redose with no dose reduction.
Grade 3	500 - < 1 000	25 000 - < 50 000	Wait until ANC ≥ 1 500 and platelets ≥ 75 000; redose with no dose reduction.
Grade 4	< 500	< 25 000	Wait until ANC ≥ 1 500 and platelets ≥ 75 000; decrease dose by 25 % or continue full dose with growth factor support.

For multiple myeloma patients treated with **DOXOLIP** in combination with bortezomib who experience PPE or stomatitis, the **DOXOLIP** dose should be modified as described in the tables for ***Palmar plantarerythrodysaesthesia*** **(Table 1)** and ***Stomatitis*** **(Table 2)** above, respectively.

Table 4 below provides the recommended schedule for other dose modification in the treatment of patients with multiple myeloma receiving **DOXOLIP** and bortezomib combination therapy.

Table 4: Dosage adjustment for DOXOLIP and bortezomib combination therapy - patients with multiple myeloma

Patient status	DOXOLIP	Bortezomib*
Fever ≥ 38 °C and ANC < 1 000/mm^3.	Do not use this cycle if before Day 4; if after Day 4, reduce next dose by 25 %.	Reduce next dose by 25 %.
On any day of medicine administration after Day 1 of each cycle: platelet count < 25 000/mm^3; haemoglobin < 8 g/dl; ANC < 500/mm^3.	Do not use this cycle if before Day 4; if after Day 4, reduce next dose by 25 % in the following cycles if bortezomib is reduced for haematologic toxicity*.	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25 % in following cycles.
Grade 3 or 4 non-haematologic medicine related toxicity.	Do not dose until recovered to Grade < 2 and reduce dose by 25 % for all subsequent doses.	Do not dose until recovered to Grade < 2 and reduce dose by 25 % for all subsequent doses.
Neuropathic pain or peripheral neuropathy.	No dosage adjustment.	Refer to package insert for bortezomib.

* For more information on bortezomib dosing and dosage adjustment, refer to the package insert for bortezomib.

Patients with impaired hepatic function

DOXOLIP dosage in patients with impaired hepatic function should be reduced based on the experience from the breast and ovarian clinical trial programs as follows:

- At initiation of therapy, if the bilirubin is between 1, 2 - 3, 0 mg/dl, the first dose is reduced by 25 %.
- If the bilirubin is > 3, 0 mg/dl, the first dose is reduced by 50 %.

If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose for cycle 2 can be increased to the next dose level, i.e. if reduced by

25 % for the first dose, increase to full dose for cycle 2; if reduced by 50 % for the first dose, increase to 75 % of full dose for cycle 2. The dosage can be increased to full dose for subsequent cycles if tolerated. **DOXOLIP** may be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to four times the upper limit of the normal range.

Evaluate hepatic function prior to **DOXOLIP** administration, using conventional clinical laboratory tests, such as: alanine aminotransferase (ALT)/aspartate aminotransferase (AST), alkaline phosphatase and bilirubin.

Patients with impaired renal function

Changes in the renal function over the range tested (estimated creatinine clearance of 30 - 156 mL/min) do not alter the pharmacokinetics of **DOXOLIP**. No pharmacokinetic data is available for patients with a creatinine clearance of less than 30 mL/min.

AIDS-KS patients with splenectomy

Treatment with **DOXOLIP** is not recommended, as there is no experience with **DOXOLIP** for patients with splenectomy.

Elderly patients

Age over the range 21 - 75 years, does not significantly alter the pharmacokinetics of **DOXOLIP**.

Method of administration

Instructions for use/handling

DO NOT USE MATERIAL THAT SHOWS EVIDENCE OF PRECIPITATION OR ANY OTHER PARTICULATE MATTER.

DOXOLIP may not be given by intramuscular or subcutaneous route (see section 4.4

Determine the dose of **DOXOLIP** to be administered (based upon the recommended dose and the patient's body surface area).

Draw up the appropriate volume of **DOXOLIP** into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agents are present in **DOXOLIP**.

The appropriate dose of **DOXOLIP** must be diluted in dextrose 5 % in water prior to administration. For doses < 90 mg, dilute **DOXOLIP** in 250 mL, and for doses ≥ 90 mg, dilute **DOXOLIP** in 500 mL of dextrose 5 % in water.

The use of any diluents other than dextrose 5 % in water for infusion, or the presence of any bacteriostatic agent, such as benzyl alcohol, may cause precipitation of **DOXOLIP**. It is recommended that **DOXOLIP** infusion line be connected through the side port of an intravenous infusion of dextrose 5 % in water. Infusion may be given through a peripheral vein. **Do not use with in-line filters**.

Caution is recommended while handling **DOXOLIP** infusion. The use of gloves is required. If **DOXOLIP** comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. **DOXOLIP** should be handled and disposed of in a manner consistent with that of other anti-cancer medicines.

4.3 Contraindications

- Patients who have a history of hypersensitivity reactions to doxorubicin hydrochloride or to any of the components of **DOXOLIP** (see section 6.1).
- Pregnancy and/or lactation (see section 4.6).
- **DOXOLIP** should not be used to treat AIDS-related KS that may be treated effectively with local therapy or systemic alpha-interferon.
- The safety and efficacy in patients under the age of 18 years have not been established.

- **DOXOLIP** should not be used in patients with pre-existing heart disease (see section 4.4).

4.4 Special warnings and precautions for use

DOXOLIP should not be given by the intramuscular or subcutaneous route.

Extravasation may result in severe local vesicant action and tissue necrosis. **DOXOLIP** should therefore be considered an irritant. If any signs or symptoms of extravasation occur (e.g. stinging, erythema) the infusion should immediately be terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction.

Infusion-related reactions

Some patients may experience an infusion-related reaction during the treatment with **DOXOLIP**, which can be serious and sometimes life threatening. These reactions may be characterised by the following: Allergic reaction,
anaphylactic reaction, asthma, facial oedema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnoea, pharyngitis, rash, pruritus, sweating, shortness of breath, tightness in the chest or throat, injection site reaction and medicine interaction.

In patients with AIDS-KS, infusion-related reactions are characterised by the following symptoms: Flushing, shortness of breath, facial oedema, headache, chills, back pain and tightness in the chest and throat. Hypotension may occur. Convulsions have been reported.

In all patients, infusion-associated reactions occurred primarily during the first infusion. Temporarily stopping the infusion usually resolves these symptoms without further therapy. Medicines to treat these symptoms (e.g. antihistamines, corticosteroids,

epinephrine (adrenalin) and anticonvulsants) as well as emergency equipment should be available for immediate use. Treatment can be resumed in most patients after all symptoms have resolved.

Infusion reactions rarely occur after the first treatment cycle with **DOXOLIP**. To minimise the risk of infusion reactions, the initial dose should be administered at a rate not greater than 1 mg/minute (see section 4.2)

Myelosuppression

In the presence of bone marrow depression, blood counts should be monitored and doses should not be repeated.

Baseline myelosuppression is observed in many patients with AIDS-KS, treated with **DOXOLIP**, due to such factors as their HIV disease or numerous concomitant medicines, or tumours involving bone marrow. Myelosuppression appears to be the dose-limiting adverse event, in patients with AIDS-KS (see section 4.8). Because of the potential for bone marrow suppression, periodic blood counts should be performed frequently during the course of

DOXOLIP therapy, and at a minimum, prior to each dose of **DOXOLIP**.

Superinfection or haemorrhage may be the result of persistent severe myelosuppression.

Secondary haematological malignancies

Secondary acute myeloid leukaemias and myelodysplasias have been reported in patients having received combined treatment with **DOXOLIP**. Therefore, any patient treated with **DOXOLIP** should be kept under haematological supervision.

Secondary oral neoplasms

Secondary oral cancer have been reported in patients with long-term (more than one year) exposure to **DOXOLIP** or those receiving a cumulative **DOXOLIP** dose greater than 720 mg/m^2. Cases of secondary oral cancer were diagnosed both during treatment with

DOXOLIP, and up to 6 years after the last dose. Patients should be examined at regular intervals for the presence or oral ulceration or any oral discomfort that may be indicative of secondary oral cancer.

Cardiac risk

All patients receiving **DOXOLIP** should routinely undergo frequent ECG monitoring. Transient ECG changes such as T-wave flattening, ST segment depression and benign dysrhythmias are not considered mandatory indications for the suspension of **DOXOLIP** therapy. However, reduction of the QRS complex is considered more indicative of cardiac toxicity. In the event of this change, the most definitive test for anthracycline myocardial injury, i.e. endomyocardial biopsy, should be considered.

More specific methods for the evaluation and monitoring of cardiac functions as compared to ECG are measurement of left ventricular ejection fraction by echocardiography or preferably by Multiple Gated Arteriography (MUGA).

These methods should be applied routinely before the initiation of **DOXOLIP** therapy and should be repeated periodically during treatment.

The evaluation of the left ventricular function is considered to be mandatory before each additional administration of **DOXOLIP** which exceeds a cumulative dose of 450 mg/m^2 of anthracyclines.

Whenever cardiomyopathy is suspected, i.e. the left ventricular ejection fraction has decreased relatively as compared to pre-treatment values and/or (at the same time) left ventricular ejection is lower than the prognostically relevant value (e.g. < 45 %), endomyocardial biopsies should be performed and the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Congestive heart failure due to cardiomyopathy may occur suddenly, without prior ECG changes and may also be encountered several weeks after discontinuation of therapy.

The evaluation tests and methods above concerning the monitoring of cardiac performance during anthracycline therapy should be employed in the following order: ECG monitoring, measurement of left ventricular ejection fraction, endomyocardial biopsy. If a test result indicates possible cardiac injury associated with **DOXOLIP** therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

Patients with a history of cardiovascular disease should not receive **DOXOLIP.**

Care should be taken in patients who have received other anthracyclines. The total dose of **DOXOLIP** should also take into account any previous (or concomitant) therapy with cardiotoxic compounds, such as other anthracyclines/anthraquinones or e.g. 5-fluorouracil. Cardiac toxicity also may occur at cumulative anthracycline doses lower than 450 mg/m^2 in patients with prior mediastinal irradiation or in patients receiving concurrent cyclophosphamide therapy.

The cardiac safety profile for the dosing schedule recommended for both breast and ovarian cancer (50 mg/m^2) is similar to the 20 mg/m^2 profile in patients with AIDS-KS (see section 4.8).

The total cumulative dose should be limited and cardiac function, including left ventricular ejection fraction, should be assessed before and monitored during treatment.

An increased incidence of congestive heart failure is associated with lifetime cumulative doses > 450 mg/m^2 or at lower doses for patients with cardiac risk factors. This should be taken into account when **DOXOLIP** is prescribed.

The recommended dose of **DOXOLIP** for AIDS-KS patients is 20 mg/m^2 every 2 to 3 weeks. The cumulative dose at which cardiotoxicity would become a concern for these patients (> 400 mg/m^2) would require more than 20 courses of **DOXOLIP** therapy over 40 to 60 weeks.

Interstitial lung disease (ILD)

Interstitial lung disease (ILD), which may have an acute onset, has been reported in patients receiving pegylated liposomal doxorubicin, including fatal cases (see section 4.8). If patients experience worsening of respiratory symptoms such as dyspnoea, dry cough, and fever, doxorubicin pegylated liposomal should be interrupted and the patient should be promptly investigated. If ILD is confirmed, doxorubicin pegylated liposomal should be discontinued and the patient treated appropriately.

Palmar-plantar erythrodysaesthesia (PPE)

Palmar-plantar erythrodysaesthesia (PPE) is the most frequent side effect (50 mg/m^2 every 4 weeks) reported for breast and ovarian cancer patients. The overall incidence of PPE reported was 44, 0 - 46, 1 %. These effects were mostly mild with severe (Grade III) cases reported in 17 - 19, 5 % of the cases. The reported incidence of life-threatening (Grade IV) cases was < 1 %. PPE infrequently resulted in permanent treatment discontinuation (3, 7 - 7, 0 %).

The symptoms of PPE include: painful, macular reddening skin eruptions. In patients experiencing these symptoms, it is generally seen after 2 - 3 cycles of treatment. In most patients it clears in 1 or 2 weeks, with or without corticosteroids treatment. For the prophylaxis and treatment of PPE, 50 - 150 mg pyridoxine per day can be used. Other strategies to prevent and treat PPE, which may be initiated 4 to 7 days after treatment with **DOXOLIP**, include keeping hands and feet cool by exposing them to cold water (soaks, baths or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting). It appears to be dose and schedule-related and can be reduced by extending the dose interval 1 to 2 weeks or reducing the dose. This reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

Stomatitis

Patients receiving continuous infusions of **DOXOLIP** may experience stomatitis. It should not interfere with patients completing therapy and no dosage adjustments are required, unless stomatitis is affecting a patient's ability to eat.

If this is the case, the dose interval may be extended by 1 or 2 weeks or the dose reduced (see section 4.2).

Patients with AIDS-KS

Haematological events may occur early in treatment with **DOXOLIP**. Haematological toxicity may require dose reduction or suspension or delay of therapy. **DOXOLIP** treatment should be temporarily suspended in patients when the absolute neutrophil count (ANC) is < 1 000/m^3 and/or the platelet count is < 50 000/mm^3. Granulocyte-colony stimulating factor (G-CSF) (or granulocyte-macrophage colony-stimulating factor (GM-CSF)) may be given as concomitant therapy to support the blood count when the ANC is < 1 000/mm^3 in subsequent cycles (see **Patients with ovarian cancer**).

Respiratory side effects occurred frequently in the AIDS population during the treatment with **DOXOLIP** and may be related to opportunistic infections. The most frequently observed opportunistic infections reported were candidiasis, cytomegalovirus, herpes simplex, *Pneumocystis jerovicii (carinii)* pneumonia and *Mycobacterium avium* complex.

All patients - other

The adverse effects of irradiation may be enhanced by doxorubicin and skin reaction previously induced by radiotherapy may occur. The dosage of **DOXOLIP** in such patients must be adjusted.

DOXOLIP should be given with great care in reduced doses to patients with hepatic impairment (see section 4.2). Dosage reduction may also be necessary in the elderly.

DOXOLIP should not be used interchangeably with other formulations of doxorubicin hydrochloride, although the difference in pharmacokinetic profiles and dosing schedules are known.

The efficacy of **DOXOLIP** combination chemotherapy has not been established in the treatment of ovarian cancer.

Sucrose

Diabetic patients should be made aware that each vial of **DOXOLIP** contains sucrose and is administered in dextrose 5 % water for intravenous infusion (see section 6.1). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not receive **DOXOLIP**.

DOXOLIP contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interactions with other medicines and other forms of interaction

- **DOXOLIP** may potentiate the toxicity of other anticancer therapies.
- In patients with solid tumours (including ovarian cancer) who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted.
- Use of liposomal doxorubicin in patients who have previously received other cardiotoxic medicines, such as daunorubicin, cyclophosphamide and idarubicin increases the risk of cardiotoxicity. Dosage adjustment of **DOXOLIP** is necessary.
- In patients with AIDS, exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with **DOXOLIP**.
- Caution must be exercised when giving any other cytotoxic medicines, especially myelotoxic medicines at the same time.

- Doxorubicin is reported to inhibit the intracellular activation of stavudine and hence its antiviral effects.
- Bone marrow depressants.
- Blood dyscrasia causing medicines.
- Vaccines (killed virus and live virus).

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of **DOXOLIP** during pregnancy or lactation is contraindicated (see section 4.3).

DOXOLIP is teratogenic in animals and should therefore not be administered during pregnancy. **DOXOLIP** can cause foetal harm when administered during pregnancy.

Male patients should be advised to use highly effective contraception, until the end of relevant systemic exposure to DOXOLIP which is a genotoxic compound including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 90 days (i.e., 60-75 days for sperm production plus 10-14 days for the transport to epididymis).

Female patients and female sexual partners of male patients receiving genotoxic anticancer medicines, should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 6 months (which covers the growth and maturation phase of folliculogenesis).

Breastfeeding

Safety and efficacy have not been established. **DOXOLIP** has a potential risk of causing adverse reactions in the infant as anthracyclines such as **DOXOLIP** are distributed in breast milk. Mothers should discontinue breastfeeding prior to the administration of **DOXOLIP**.

4.7 Effects on ability to drive and use machines

Dizziness and somnolence are infrequently associated with **DOXOLIP** administration. Patients suffering from these effects should avoid driving motor vehicles and/or operating machinery.

4.8 Undesirable effects

Infections and infestations

Frequent: Folliculitis, fungal infection, cold sores (non-herpetic), upper respiratory tract infection, pharyngitis, oral moniliasis, herpes zoster, urinary tract infection, infection, opportunistic infections (such as candidiasis, cytomegalovirus, herpes simplex, *Pneumocystis carinii* pneumonia and *Mycobacterium avium* complex),

Blood and the lymphatic system disorders

Frequent: Thrombocytopenia, neutropenia, anaemia, leukopenia, thrombocythaemia, hypochromic anaemia, febrile neutropenia, lymphopenia, myelosuppression

Less frequent: Reduction in haemoglobin and platelets

Frequency unknown: Life threatening (grade IV) haematological effects, sepsis, sepsis related to leukopenia Myelosuppression is mostly mild or moderate. Life threatening (grade IV) haematological effects were reported. Growth factor support was required infrequently (< 5 %) and transfusion support was required in approximately 15 %of patients (see section 4.2).

Immune system disorders

Frequent: Hypersensitivity reactions (including anaphylactic reactions)

Metabolism and nutrition disorders

Frequent: Anorexia, dehydration, cachexia, decreased appetite, hypokalaemia, hyperkalaemia, hypomagnesaemia, hyponatraemia, hypocalcaemia

Less frequent: Tumour lysis syndrome

Psychiatric disorders

Frequent: Anxiety, depression, insomnia

Less frequent: Confusion

Nervous system disorders

Frequent: Peripheral neuropathy, paraesthesia, hypaesthesia, dysaesthesia, headache, dizziness, neuropathy, hypertonia, somnolence, peripheral sensory neuropathy, neuralgia, polyneuropathy, dysgeusia

Eye disorders

Frequent: Lacrimation, blurred vision, conjunctivitis, retinitis

Cardiac disorders

Frequent: Ventricular dysrhythmia, cardiovascular disorder, chest pain

Less frequent: Electrocardiogram (ECG) abnormalities, heart failure, and dysrhythmia

Vascular disorders

Frequent: Vasodilatation, hypotension, orthostatic hypotension, flushing, hypertension, phlebitis, syncope

Less frequent: Thrombophlebitis

Respiratory, thoracic and mediastinal disorders

Frequent: Epistaxis, dyspnoea, nasopharyngitis, upper respiratory tract infection, cough, exertional dyspnoea, musculoskeletal chest pain

Frequency not known: Interstitial lung disease

Gastrointestinal disorders

Frequent: Mucositis, stomatitis, oral pain, nausea, vomiting, constipation, diarrhoea, abdominal pain, dyspepsia, mouth ulceration, oesophagitis, gastritis, dysphagia, dry mouth, flatulence, gingivitis, taste perversion, aphthous stomatitis, and glossitis

Hepatobiliary disorders

Less frequent: Hepatic damage (see ***Investigations*** below)

Skin and subcutaneous tissue disorders

Frequent: Bullous eruptions, dermatitis, erythematosus rash, nail disorder, scaly skin, palmar-plantar erythrodysaesthesia (PPE) (see section 4.4), dry skin, alopecia, abnormal pigmentation, vesiculobullous rash, pruritus, exfoliative dermatitis, skin disorder, maculopapular rash, sweating, acne, skin ulcer, rash, skin hyperpigmentation

Less frequent: Hyperpigmentation of oral mucosa or nails, onycholysis

Musculoskeletal, connective tissue and bone disorders

Frequent: Leg cramps, bone pain, musculoskeletal pain, pain, myalgia, arthralgia, muscle spasms, muscular weakness

Renal and urinary disorders

Frequent: Dysuria

Less frequent: Renal damage (see ***Investigations*** below)

Reproductive system and breast disorders

Frequent: Breast pain, vaginitis, scrotal erythema

Less frequent: Genotoxicity in males and females

General disorders and administrative site conditions

Frequent: Oedema, leg oedema, asthenia, fatigue, pyrexia, weakness, pain, chills, malaise, peripheral oedema, mucous membrane disorder, lethargy, pain in extremities, influenza-like illness, hyperthermia, and infusion associated acute reactions

Investigations

Frequent: Weight loss, increased AST/ALT, decreased ejection fraction, increased blood creatinine, increased alkaline phosphate

Less frequent: Increased bilirubin, sepsis related to leukopenia, hyperuricaemia

Increases in AST and bilirubin (may be related to the underlying disease and not **DOXOLIP**).

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the Holder of certificate of registration via email: pharmacovigilance.africasme@sunpharma.com or Tel: +27(0) 12 643 2000.

4.9 Overdose

See sections 4.4 and 4.8.

Acute overdosage with **DOXOLIP** worsens the toxic effect of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage of the severely myelosuppressed patient consists of hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

5. PHARMACOLOGICAL PROPERTIES

A.26 Cytostatic agents

5.1 Pharmacodynamic properties

Doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius*var *caesius*.

The exact mechanism of the antitumour activity of doxorubicin is unknown. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effect. This may be the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix, therefore preventing their unwinding for replication.

5.2 Pharmacokinetic properties

Distribution:

2 During circulation, at least 90 % of liposomal doxorubicin remains encapsulated. This results in a large area under the plasma concentration-time curve (AUC) of 277 and 590 µg per mL (µg/mL) per hour for doses of 10 and 20 mg/m^2 respectively, with a prolonged circulation in the plasma, with relatively little tissue distribution, but tumour neovasculature is reported to permit penetration of liposomes into tumour tissue.

Half-life:

First phase half-lives: 4, 7 and 5, 2 hours for doses of 10 and 20 mg/m^2, respectively.

Second phase half-lives: 52, 3 and 55 hours for doses of 10 and 20 mg/m^2, respectively.

Elimination:

Renal elimination of liposomal doxorubicin is slower than elimination of the standard doxorubicin: 5, 5 % of an injected dose of liposomal doxorubicin being recoverable in urine after 72 hours, compared with 11 % of an injected dose of standard doxorubicin after only 24 hours.

Special patient populations

Breast cancer patients:

The mean intrinsic clearance is 0,016 l/h/m^2, the mean central volume of distribution is 1, 46 l/m^2. The mean apparent half-life is 71, 5 hours.

Ovarian cancer patients:

The pharmacokinetics of liposomal doxorubicin at higher doses is non-linear and exposure is expected to be longer than at lower doses. The mean intrinsic clearance is 0,021 l/h/m, the mean central volume of distribution is 1, 952 l/m^2. The mean apparent half-life is 75, 0 hours.

In the dose range 10 to 20 mg/m^2, liposomal doxorubicin displays linear pharmacokinetics. After liposomal doxorubicin administration, disposition occurred in two phases, with a relatively short first phase (approximately 5 hours) and a prolonged second phase (approximately 55 hours) that accounted for the majority of the area under the curve (AUC).

AIDS-related Kaposi's sarcoma (KS) patients:

The plasma pharmacokinetic parameters of liposomal doxorubicin (primarily representing pegylated liposomal doxorubicin hydrochloride and low levels of unencapsulated doxorubicin hydrochloride) observed after 20 mg/m^2 doses are presented in the table below:

Pharmacokinetic parameters in liposomal doxorubicin-treated AIDS-KS patients	
Parameter	**Mean ± Standard error 20 mg/m^2 (n=23)**
Maximum plasma concentration * (µg/mL)	8,34 ± 0,49
Plasma clearance (l/h/m^2)	0,041 ± 0,004
Volume of distribution (l/m^2)	2,72 ± 0,120
AUC (µg/mL.h)	590 ± 58,7

λ1 half-life (hours)	5,2 ± 1,4
λ2 half-life (hours)	55,0 ± 4,8

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active ingredient

Doxorubicin

Inactive ingredients

Ammonium sulphate, cholesterol, ethyl alcohol, histidine, hydrogenated soy phosphatidyl choline, *N*-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt, sucrose, water for injection.

6.2 Incompatibilities

DO NOT MIX DOXOLIP WITH OTHER MEDICINES.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store between 2 °C to 8 °C.

Do not freeze. Keep vials in outer carton until required for use.

Discard any unused portion.

KEEP OUT OF REACH OF CHILDREN.

After dilution with dextrose 5 % in water for intravenous infusion, the diluted **DOXOLIP** solution should be used immediately.

Diluted product not for immediate use should be stored between 2 °C to 8 °C for no longer than 24 hours. Partially used vials should be discarded.

6.5 Nature and contents of container

DOXOLIP is packed in a 10 mL colourless USP type I glass vial with a 20 mm grey bromobutyl rubber stopper, sealed with a 20 mm light blue aluminium flip off seal.

One vial is packed per outer carton.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

43/26/0018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 5 December 2013.

10. DATE OF REVISION OF THE TEXT

30 July 2024

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