1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

DOXOPEG (liposomal infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the liposomal infusion contains 2 mg of doxorubicin hydrochloride.

Contains sugar: sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Liposomal infusion.

A red, translucent, sterile and pyrogen-free suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer:

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

Ovarian cancer:

DOXOPEG is indicated for the treatment of advanced ovarian cancer in women where a first line platinum-based chemotherapy regimen has failed.

Multiple myeloma:

DOXOPEG 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 sarcoma (KS):

DOXOPEG is indicated for AIDS-related Kaposi's sarcoma (KS) in patients with low CD_4 counts (< 200 CD_4 lymphocytes per mm^3) and extensive mucocutaneous or visceral disease.

4.2 Posology and method of administration

Posology

DOXOPEG must not be given by intramuscular or subcutaneous route.

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

DOXOPEG exhibits unique pharmacokinetic properties and should not be used interchangeably with other formulations of doxorubicin hydrochloride (see section 4.4).

Treatment of breast cancer or ovarian cancer:

DOXOPEG 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 DOXOPEG in 250 ml dextrose 5 % in water.

Doses ≥ 90 mg: dilute DOXOPEG in 500 ml dextrose 5 % in water.

The initial dose is administered at a rate < 1 mg/minute, in order to minimise the risk of infusion reactions.

If no infusion reaction is observed, subsequent DOXOPEG 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:

DOXOPEG 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 DOXOPEG in 250 ml of 5 % (50 mg/ml) glucose solution for infusion.

Doses ≥ 90 mg: dilute DOXOPEG 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 administration 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 DOXOPEG 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 DOXOPEG will be administered over 1 hour, as tolerated. If an infusion reaction to DOXOPEG occurs, stop the infusion. After the symptoms have resolved, attempt to administer remaining DOXOPEG 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:

DOXOPEG should be administered intravenously at 20 mg/m^2 every 2 - 3 weeks. Intervals shorter than 10 days should be avoided, as accumulation of DOXOPEG 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 the therapeutic response.

DOXOPEG, 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-medication (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 DOXOPEG 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.

DOXOPEG must not be given by the intramuscular or subcutaneous route.

Do not use with in-line filters.

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

The toxicity grading in these tables is based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

The tables for PPE and stomatitis provide the schedule followed for dose modification in clinical trials in the treatment of breast or ovarian cancer (modification of the recommended 4-week treatment cycle): If these toxicities occur in patients with AIDS-related KS, the recommended 2-to-3-week treatment cycle can be modified in a similar manner.

The table for haematological toxicity provides the schedule followed for dose modification in clinical trials in the treatment of patients with breast or ovarian cancer only (see section 4.8 for dose modification in patients with AIDS-KS).

Palmar-plantar erythrodysaesthesia:

	Week after prior DOXOPEG dose		
Toxicity grade after prior DOXOPEG dose	**Week 4**	**Week 5**	**Week 6**
Grade 1: Mild erythema, swelling, or desquamation not interfering with daily activities.	Re-dose unless patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week.	Re-dose 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	Wait an additional week.	Wait an additional week.	Decrease dose by 25 %; return to 4-week interval.

physical activities; small blisters or ulcerations less than 2 cm in diameter.			
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.

Stomatitis:

	Week after prior DOXOPEG dose		
Toxicity grade after prior DOXOPEG dose	**After week 4**	**After week 5**	**After week 6**
Grade 1: Painless ulcers, erythema, or mild soreness.	Re-dose unless patient has experienced a previous grade 3 or 4 stomatitis, in which case wait	Re-dose unless patient has experienced a previous grade 3 or 4 stomatitis, in which case wait	Decrease dose by 25 %; return to 4-week interval or withdraw patient per health

	an additional week.	an additional week.	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 health practitioner's assessment.
Grade 3: Painful erythema, oedema, or ulcers, and 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.

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

Grade	ANC	Platelets	Modification
1	1500 - 1900	75 000 – 150 000	Resume treatment with no dose reduction.
2	1000 < 1500	50 000 < 75 000	Wait until ANC ≥ 1500 and platelets ≥ 75 000; re-

			dose with no dose reduction.
3	500 < 1000	25 000 < 50 000	Wait until ANC ≥ 1500 and platelets ≥ re-dose with no dose reduction.
4	< 500	< 25 000	Wait until ANC ≥ 1500 and platelets ≥ 75 000; decrease dose by 25 % or continue full dose with growth factor support.

For multiple myeloma patients treated with DOXOPEG in combination with bortezomib who experience PPE or stomatitis, the DOXOPEG dose should be modified as described in the tables for ***Palmar-plantar erythrodysaesthesia*** and ***Stomatitis*** above respectively. For more detailed information on bortezomib dosing and dosage adjustments, refer to the package insert for bortezomib.

Dosage adjustment for DOXOPEG and bortezomib combination therapy - patients with multiple myeloma:

Patient status	**DOXOPEG**	**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 professional information for bortezomib.

Special populations:

Patients with impaired hepatic function:

DOXOPEG dosage in patients with an 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. DOXOPEG 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 DOXOPEG 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 DOXOPEG.

No pharmacokinetic data are available for patients with a creatinine clearance less than 30 ml/min.

AIDS-KS patients with splenectomy:

Treatment with DOXOPEG is not recommended, as there is no experience with DOXOPEG in patients with splenectomy.

Elderly patients:

Age across the range of 21 – 75 years, does not significantly alter the pharmacokinetics of DOXOPEG.

Method of administration

DOXOPEG is for intravenous use only.

Instructions for the use/handling:

- **DO NOT USE MATERIAL THAT SHOWS EVIDENCE OF PRECIPITATION OR ANY OTHER PARTICULATE MATTER**.
- DOXOPEG may not be given by intramuscular or subcutaneous route.
- Determine the dose of DOXOPEG to be administered (based upon the recommended dose and the patient's body surface area).
- Draw up the appropriate volume of DOXOPEG into a sterile syringe.
- Aseptic technique must be strictly observed, since no preservative or bacteriostatic agents are present in DOXOPEG.
- The appropriate dose of DOXOPEG must be diluted in dextrose 5 % in water prior to administration. For doses < 90 mg, dilute DOXOPEG in 250 ml, and for doses ≥ 90 mg, dilute DOXOPEG 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 DOXOPEG.

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

Incompatibilities:

DO NOT MIX DOXOPEG WITH OTHER MEDICINES.

4.3 Contraindications

- Hypersensitivity to doxorubicin hydrochloride, or to any of the excipients (see section 6.1).
- Pregnancy and/or lactation (see section 4.6).
- DOXOPEG 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 (see section 4.4).

4.4 Special warnings and precautions for use

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

Myelosuppression:

DOXOPEG causes pronounced bone marrow depression, which may be dose limiting. White cell counts reach a nadir 10 to 15 days after a dose and usually recovers by about 21 days.

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

DOXOPEG should be given with great care in reduced doses to patients with hepatic impairment.

Baseline myelosuppression is observed in many patients with AIDS-KS treated with DOXOPEG, due to factors such as their HIV disease, numerous concomitant medicines or tumours involving bone marrow. Myelosuppression appears to be a 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 DOXOPEG therapy, and at a minimum, prior to each dose of DOXOPEG.

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

DOXOPEG 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 DOXOPEG combination chemotherapy has not been established in the treatment of ovarian cancer.

Cardiac risk:

The anthracyclines, such as DOXOPEG, may produce cardiotoxicity, such as electrocardiogram (ECG) abnormalities, dysrhythmias or congestive heart failure, which may be fatal.

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

Patients are at increased risk of thromboembolic disease. Thrombophlebitis and venous thrombosis, as well as pulmonary embolism, may occur less frequently.

More specific methods for the evaluation and monitoring of cardiac function, 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 DOXOPEG 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 DOXOPEG which exceeds a cumulative dose of 450 mg/m^2.

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 are lower than 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 (CHF) due to cardiomyopathy may occur suddenly, without prior ECG changes, and may also be encountered several weeks after discontinuation of therapy. The CHF may be irreversible and sometimes fatal.

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 and endomyocardial biopsy. If a test result indicates possible cardiac injury associated

with DOXOPEG therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

Patients with a history of cardiovascular disease should receive DOXOPEG only when the benefit outweighs the risk to the patient. Caution should be exercised in patients with impaired cardiac function who receive DOXOPEG. The most important determinant of cardiotoxicity occurred with total doses greater than 450 to 550 mg/m^2 and may occur months or even years after use.

Care should be taken in patients who have received other anthracyclines.
The total cumulative dose should be limited and cardiac function should be monitored during treatment.

The total cumulative dose of DOXOPEG should also take into account any previous (or concomitant) therapy with cardiotoxic compounds, such as other anthracyclines/anthraquinones or 5-fluorouracil. Cardiotoxicity may also occur at cumulative anthracycline doses lower than 450 mg/m^2 in patients with prior mediastinal irradiation or in patients receiving concurrent cyclophosphamide, trastuzumab or other antineoplastic therapy. CHF has been reported, even with doses of 240 to 300 mg/m^2.

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). Cardiotoxicity is more likely to occur in children, elderly patients and in patients with liver disease or trisomy 21. High single doses are more toxic than lower, more frequent doses.

Palmar-plantar erythrodysaesthesia (PPE):

The symptoms of PPE include painful, macular reddening skin eruptions. It is generally seen after 2 – 3 cycles of treatment in patients experiencing these symptoms. In most patients it clears in 1 or 2 weeks, with or without treatment of corticosteroids.

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 DOXOPEG, 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).

PPE appears to be dose and schedule-related and can be reduced by extending the dose interval 1 to 2 weeks or by reducing the dose.

This reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

Patients with AIDS-KS:

Haematological events may occur early in treatment with DOXOPEG.

Haematological toxicity may require dose reduction, suspension or delay of therapy.

DOXOPEG 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. G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC is < 1 000/mm^3 in subsequent cycles.
The haematological toxicity for ovarian cancer patients is less severe than in AIDS-KS setting (see section 4.8).

Respiratory side effects occurred frequently in the AIDS population during treatment with DOXOPEG and may be related to opportunistic infections (see section 4.8).

Secondary haematological malignancies:

As with other DNA-damaging antineoplastic agents, secondary acute myeloid leukemias and myelodysplasias have been reported in patients having received combined treatment with doxorubicin. Therefore, any patient treated with DOXOPEG should be kept under haematological supervision.

Secondary oral neoplasms:

Very rare cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to DOXOPEG pegylated liposomal or those receiving a cumulative DOXOPEG dose greater than 720 mg/m^2.

Cases of secondary oral cancer were diagnosed both, during treatment with DOXOPEG, and up to 6 years after the last dose. Patients should be examined at regular intervals for the presence of oral ulceration or any oral discomfort that may be indicative of secondary oral cancer.

Infusion-associated reactions:

Serious and sometimes life-threatening infusion reactions, which are characterised by allergic-like or anaphylactoid-like reactions, with symptoms including asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial oedema, chills, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of DOXOPEG. Very rarely, convulsions also have been observed in relation to infusion reactions. Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g., antihistamines, corticosteroids, adrenaline, and anticonvulsants), as well as emergency equipment should be available for immediate use. In most patients, treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. To

minimise the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute.

Extravasation:

Although local necrosis following extravasation has been reported very rarely, DOXOPEG is considered to be an irritant. Animal studies indicate that administration of doxorubicin hydrochloride as a liposomal formulation reduces the potential for extravasation injury. If any signs or symptoms of extravasation occur (e.g., stinging, erythema) terminate the infusion immediately and restart in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. DOXOPEG must not be given by the intramuscular or subcutaneous route.

Diabetic patients:

It should be noted that each vial of DOXOPEG contains sucrose (see section 2 and ***Sucrose*** below) and is administered in dextrose 5 % water for intravenous infusion.

Interstitial lung disease (ILD):

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

promptly investigated. If ILD is confirmed, DOXOPEG should be discontinued and the patient treated appropriately.

Sucrose:

DOXOPEG contains sucrose (see section 2). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take DOXOPEG.

4.5 Interaction with other medicines and other forms of interaction

- Although not formally studied, DOXOPEG may potentiate the toxicity of other anti-cancer therapies.
- In patients with solid tumours (including ovarian cancer), who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted.
- In patients with AIDS-KS, exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with DOXOPEG.
- Caution must be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

4.6 Fertility, pregnancy and lactation

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

Women of child-bearing potential/contraception in men and women:

Due to the genotoxic potential of doxorubicin hydrochloride, women of child-bearing potential should use effective contraceptive measures while being treated with DOXOPEG pegylated liposomal and for 8 months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving DOXOPEG pegylated liposomal and for 6 months following completion of treatment.

Pregnancy:

DOXOPEG is teratogenic in animals and should therefore not be administered during pregnancy.

DOXOPEG can cause foetal harm when administered during pregnancy.

Lactation:

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of adverse effects

The most frequent adverse reactions (≥ 20 %) were neutropenia, nausea, leukopenia, anaemia, and fatigue.

Severe adverse reactions (Grade 3/4 adverse reactions occurring in ≥ 2 % of patients) were neutropenia, PPE, leukopenia, lymphopenia, anaemia, thrombocytopaenia, stomatitis, fatigue, diarrhoea, vomiting, nausea, pyrexia, dyspnoea, and pneumonia. Less frequently reported severe adverse reactions included *Pneumocystis jirovecii* pneumonia, abdominal pain, cytomegalovirus infection including cytomegalovirus chorioretinitis, asthenia, cardiac arrest, cardiac failure, cardiac failure congestive, pulmonary embolism, thrombophlebitis, venous thrombosis, anaphylactic reaction, anaphylactoid reaction, toxic epidermal necrolysis, and Stevens-Johnson syndrome.

b) Tabulated list of adverse reactions

The following side effects have been reported in patients receiving DOXOPEG in patients for the treatment of breast cancer, ovarian cancer, multiple myeloma, and AIDS-related KS. Post-marketing adverse reactions are also included.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Sepsis, pneumonia,

MedDRA system organ class	Frequency	Adverse reactions
		Pneumocystis jirovecii pneumonia, cytomegalovirus infection including cytomegalovirus chorioretinitis, mycobacterium avium complex infection, candidiasis, herpes zoster, urinary tract infection, infection, upper respiratory tract infection, oral candidiasis, oral monoliasis, folliculitis, pharyngitis, nasopharyngitis.
	Less frequent	Herpes simplex, fungal infection, opportunistic infection (including *aspergillus, histoplasma, isospora, legionella, microsporidium, salmonella, staphylococcus, toxoplasma, tuberculosis)*[a]

MedDRA system organ class	**Frequency**	**Adverse reactions**
Neoplasms benign, malignant and unspecified	Frequency unknown	Acute myeloid leukaemia[b], myelodysplastic syndrome[b], oral neoplasm[b]
Blood and lymphatic system disorders	Frequent	Leukopenia, neutropenia, lymphopenia, anaemia (including hypochromic), thrombocytopaenia, febrile neutropenia
	Less frequent	Pancytopenia, thrombocytosis, bone marrow failure
	Frequency unknown:	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	Less frequent	Hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Metabolism and nutrition	Frequent	Decreased appetite, cachexia,

MedDRA system organ class	**Frequency**	**Adverse reactions**
disorders		dehydration, hypokalaemia, hyponatraemia, hypocalcaemia
	Less frequent	Hyperkalaemia, hypomagnesaemia, hyperuricaemia, tumour lysis syndrome.
Psychiatric disorders	Frequent	Confusional state, anxiety, depression, insomnia
Nervous system disorders	Frequent	Neuropathy peripheral, peripheral sensory neuropathy, neuralgia, paraesthesia, hypoaesthesia, dysgeusia, headache, lethargy, dizziness
	Less frequent	Polyneuropathy, convulsion, syncope, dysaesthesia, somnolence
Eye disorders	Frequent	Conjunctivitis, retinitis
	Less frequent	Vision blurred, lacrimation increased, retinitis
Cardiac disorders	Frequent	Tachycardia

MedDRA system organ class	Frequency	Adverse reactions
	Less frequent	Palpitations, cardiac arrest, cardiac failure, cardiac failure congestive, cardiomyopathy, cardiotoxicity, dysrhythmia, including ventricular dysrhythmia, bundle branch block right, conduction disorder, atrioventricular block, cyanosis
Vascular disorders	Frequent	Hypertension, hypotension, flushing, syncope
	Less frequent	Pulmonary embolism, infusion site necrosis (including soft tissue necrosis and skin necrosis), phlebitis, orthostatic hypotension, thrombophlebitis, venous thrombosis, vasodilatation
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, dyspnoea exertional, epistaxis, cough
	Less frequent	Asthma, chest discomfort, throat tightness

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Not known	Interstitial lung disease
Gastrointestinal disorders	Frequent	Stomatitis (including aphthous), nausea, vomiting, diarrhoea, constipation, gastritis, aphthous stomatitis, mouth ulceration, dyspepsia, dysphagia, oesophagitis, abdominal pain, abdominal pain upper, oral pain, dry mouth, mucositis, taste perversion
	Less frequent	Flatulence, gingivitis, glossitis, lip ulceration
Hepatobiliary disorders	Less frequent	Hepatic damage
Skin and subcutaneous tissue disorders	Frequent	Palmar plantar erythrodysaesthesia syndrome[a], rash (including erythematous, maculo-papular, and papular), alopecia, skin exfoliation, blister, dry skin, scaly skin, erythema, pruritus, hyperhidrosis, skin

MedDRA system organ class	Frequency	Adverse reactions
		hyperpigmentation, medicine eruption
	Less frequent	Dermatitis, dermatitis exfoliative, acne, skin ulcer, dermatitis allergic, urticaria, skin discolouration, petechiae, pigmentation disorder, nail disorder, toxic epidermal necrolysis, erythema multiforme, dermatitis bullous, lichenoid keratosis, onycholysis, hyperpigmentation of the oral mucosa or nails
	Frequency unknown	Stevens-Johnson syndrome[b]
Musculoskeletal and connective tissue disorders	Frequent	Musculoskeletal pain (including musculoskeletal chest pain, back pain, pain in extremity), muscle spasms, myalgia, arthralgia, bone pain

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Less frequent	Muscular weakness
Reproductive system and breast disorders	Frequent	Breast pain
	Less frequent	Vaginal infection, scrotal erythema
Renal and urinary disorders	Frequent	Dysuria
	Less frequent	Breast pain, vaginal infection, scrotal erythema, renal damage
General disorders and administration site conditions	Frequent	Pyrexia, fatigue, lethargy, infusion-related reaction, pain, pain in extremities, chest pain, influenza-like illness, chills, fever, mucosal inflammation, asthenia, malaise, oedema, leg oedema, oedema peripheral
	Less frequent	Administration site extravasation, injection site reaction, face oedema, hyperthermia, mucous membrane disorder
Investigations	Frequent	Weight decreased

MedDRA system organ class	Frequency	Adverse reactions
	Less frequent	Ejection fraction decreased, liver function test abnormal (including blood bilirubin increased, alanine aminotransferase increased and aspartate aminotransferase increased), blood creatinine increased
Injury, poisoning and procedural complications	Less frequent	Radiation recall phenomenon[a]
[a]See Description of selected adverse reactions [b]Post-marketing adverse reaction		

c) Description of selected adverse reactions

Palmar plantar erythrodysaesthesia:

The most frequent undesirable effect reported in breast/ovarian clinical trials was palmar-plantar erythrodysesthesia (PPE). The overall incidence of PPE reported was 41,3 % and 51,1 % in the ovarian and breast clinical trials, respectively. These effects were mostly mild, with severe (grade 3) cases reported in 16,3 % and 19,6 % of patients. The reported incidence of life-threatening (grade 4) cases was < 1 %. PPE infrequently resulted in permanent treatment discontinuation (1,9 % and 10,8 %). PPE was reported in 16 % of multiple myeloma patients treated with

doxorubicin plus bortezomib combination therapy. Grade 3 PPE was reported in 5 % of patients. No grade 4 PPE was reported. The rate of PPE was substantially lower in the AIDS-KS population (1,3 % all grade, 0,4 % grade 3 PPE, no grade 4 PPE). See section 4.4.

Opportunistic infections:

Respiratory undesirable effects frequently occurred in clinical studies of doxorubicin and may be related to opportunistic infections (OI's) in the AIDS population. Opportunistic infections are observed in KS patients after administration with doxorubicin, and are frequently observed in patients with HIV induced immunodeficiency. The most frequently observed OI's in clinical studies were candidiasis, cytomegalovirus, herpes simplex, Pneumocystis jirovecii pneumonia, and mycobacterium avium complex.

Cardiac toxicity:

An increased incidence of congestive heart failure is associated with doxorubicin therapy at cumulative lifetime doses >450 mg/m^2 or at lower doses for patients with cardiac risk factors. Endomyocardial biopsies on nine of ten AIDS-KS patients receiving cumulative doses of doxorubicin greater than 460 mg/m^2 indicate no evidence of anthracycline-induced cardiomyopathy. The recommended dose of doxorubicin for AIDS-KS patients is 20 mg/m^2 every two-to-three weeks. The cumulative dose at which cardiotoxicity would become a concern for these AIDS-KS patients (> 400 mg/m^2) would require more than 20 courses of doxorubicin therapy over 40 to 60 weeks.

In addition, endomyocardial biopsies were performed in 8 solid tumour patients with cumulative anthracycline doses of 509 mg/m^2 –1,680 mg/m^2 . The range of Billingham cardiotoxicity scores was grades 0-1,5. These grading scores are consistent with no or mild cardiac toxicity.

In the pivotal phase III trial versus doxorubicin, 58/509 (11,4 %) randomised subjects (10 treated with doxorubicin at a dose of 50 mg/m^2 /every 4 weeks versus 48 treated with doxorubicin at a dose of 60 mg/m^2 /every 3 weeks) met the protocol-defined criteria for cardiac toxicity during treatment and/or follow-up. Cardiac toxicity was defined as a decrease of 20 points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 points or greater if the LVEF became abnormal (less than the lower limit for normal). None of the 10 doxorubicin subjects who had cardiac toxicity by LVEF criteria developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin subjects who had cardiac toxicity by LVEF criteria also developed signs and symptoms of CHF.

In patients with solid tumours, including a subset of patients with breast and ovarian cancers, treated at a dose of 50mg/m^2 /cycle with lifetime cumulative anthracycline doses up to 1,532 mg/m^2, the incidence of clinically significant cardiac dysfunction was low. Of the 418 patients treated with doxorubicin 50 mg/m^2 /cycle, and having a baseline measurement of left ventricular ejection fraction (LVEF) and at least one follow-up measurement assessed by MUGA scan, 88 patients had a cumulative anthracycline dose of > 400 mg/m^2 , an exposure level associated with an increased risk of cardiovascular toxicity with conventional doxorubicin. Only 13 of these 88 patients (15 %) had at least one clinically

significant change in their LVEF, defined as an LVEF value less than 45 % or a decrease of at least 20 points from baseline. Furthermore, only 1 patient (cumulative anthracycline dose of 944 mg/m^2), discontinued study treatment because of clinical symptoms of congestive heart failure.

Radiation recall phenomenon:

Recall of skin reaction due to prior radiotherapy has occurred less frequently with doxorubicin administration.

Infusion-related reactions:

Some patients may experience an infusion-related reaction during the treatment with DOXOPEG, which can be serious and sometimes life-threatening. These are characterised by the following symptoms: 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.

Infusion-associated reactions occur primarily during the first infusion. Temporarily stopping the infusion usually resolves these symptoms without further therapy. Medications 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 may occur after the first treatment cycle with DOXOPEG.

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).

Stomatitis:

Patients receiving continuous infusions of DOXOPEG 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).

Local reactions:

Local necrosis following extravasation has been reported, but the frequency is unknown. DOXOPEG should therefore be considered an irritant. If any signs or symptoms of extravasation occur (e.g. stinging, erythema), the infusion should be immediately 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. Serious skin reactions, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis may occur less frequently.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8.

Acute overdosage with DOXOPEG 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

5.1 Pharmacodynamic properties

Pharmacological Classification: A 26. Cytostatic agents.

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances), ATC code: L01DB01.

Doxorubicin is an anthracycline cytostatic antibiotic with activity against a variety of malignancies, including Kaposi's sarcoma (KS). DOXOPEG is a liposome formulation which is encapsulated in liposomes with surface bound

methoxypolyethylene glycol (MPEG). This process is known as pegylation and protects liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time. Liposomal doxorubicin has shown to inhibit the growth of KS cells *in vitro* and *in vivo*.

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 replication.

5.2 Pharmacokinetic properties

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^2 and the mean central volume of distribution is 1,95 L/m^2. The mean apparent half-life is 75,0 hours.

In the dose range 10 to 20 mg/m^2, liposomal doxorubicin displayed 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 accounts for the majority of the area under the curve (AUC).

AIDS-related Kaposi sarcoma (KS) patients:

The 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 administered by a 30-minute infusion, 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)	52 ± 1,4
λ2 half-life (hours)	55,0 ± 4,8

* Measured at the end of a 30 minute infusion

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonium sulphate

Cholesterol

Ethanol

Histidine

Hydrogenated soy phosphatidyl choline

Methoxypolyethylene glycol 2000 (MPEG 2000)

Sucrose

Water for injection

6.2 Incompatibilities

DOXOPEG must not be mixed with other medicines except those mentioned in section 4.2.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store between 2 to 8 °C.

Do not freeze.

Keep the vials in the outer carton until required for use.

After dilution:

After dilution with dextrose 5 % in water for intravenous infusion, the diluted DOXOPEG solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Diluted product not for immediate use should be stored between 2 to 8 °C for no longer than 24 hours.

For single use only.

Discard any remaining solution.

6.5 Nature and contents of container

The container is a Type 1, clear glass, 15 ml vial, with a grey Teflon stopper, an aluminium seal and red plastic flip-off cap.

The DOXOPEG vial is packed in an outer carton.

DOXOPEG is supplied as a single pack or packs of ten vials.

Each 15 ml vial of DOXOPEG contains 10 ml doxorubicin hydrochloride 2 mg/ml.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements. See also section 4.2.

7 HOLDER OF CERTIFICATE OF REGISTRATION

KEY ONCOLOGICS (PTY) LTD

39 Eleventh Avenue

Houghton Estate

2198

Johannesburg

South Africa

8 REGISTRATION NUMBER

A40/26/0389

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 May 2014

10 DATE OF REVISION OF THE TEXT

7 August 2024