

**APPROVED PROFESSIONAL INFORMATION:
DR. REDDY'S LABORATORIES (PTY) LTD.
SOPILCIN 20 mg/10 ml & 50 mg/25 ml
(SOLUTION FOR INFUSION)**

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SOPILCIN 20 mg/10 ml, 20 mg/10 ml, Concentrate for infusion

SOPILCIN 50 mg/25 ml, 50 mg/25 ml, Concentrate for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOPILCIN, a liposome formulation, is doxorubicin hydrochloride 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.

Each SOPILCIN vial contains 2 mg/ml doxorubicin hydrochloride in a pegylated liposomal formulation and delivers 10 ml (20 mg) or 25 ml (50 mg) in a concentrate for infusion for single intravenous use and is presented as a sterile, translucent, red suspension. The active ingredient of SOPILCIN is doxorubicin HCl, a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*.

Excipients with known effect

Contains fully hydrogenated soy phosphatidylcholine (from soyabean) – see section 4.3

Contains less than 1 mmol sodium (23 mg) per dose, and is essentially 'sodium-free'.

SOPILCIN 20 mg/ 10 ml: Contains sugar (sucrose) 940 mg/10 ml.

SOPILCIN 50 mg/25 ml: Contains sugar (sucrose) 2350 mg/25 ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for infusion.

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The suspension is translucent and red.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SOPILCIN is indicated:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.
- For the treatment of advanced ovarian cancer in women who have failed a first line platinum-based chemotherapy regimen.
- 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.
- For AIDS-related Kaposi's sarcoma (KS) in patients with low CD₄ counts (< 200 CD₄ lymphocytes/mm³) and extensive mucocutaneous or visceral disease.

4.2 Posology and method of administration

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

SOPILCIN exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride (see sections 4.4 and 5.2).

Posology

Breast cancer/ Ovarian cancer:

SOPILCIN is administered intravenously at a dose of 50 mg/m² once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

Multiple myeloma:

SOPILCIN is administered at 30 mg/m² 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/m² on days 1; 4; 8 and 11 every 3 weeks. The dose should be

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repeated as long as patients respond satisfactorily and tolerate treatment.

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 SOPILCIN should be administered over 90 minutes (see "Method of Administration").

AIDS-KS patients:

SOPILCIN should be administered intravenously at 20 mg/m² every 2 to 3 weeks.

Avoid intervals shorter than 10 days as medicine accumulation and increased toxicity cannot be ruled out. Patients should be treated for 2 to 3 months to achieve a therapeutic response. Treatment should be continued as needed to maintain a therapeutic response.

All patients:

If the patient experiences early signs or symptoms of infusion reaction (see sections 4.4 and 4.8), immediately discontinue the infusion, give appropriate pre-medications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

To manage adverse events such as palmar-plantar erythrodysesthesia (PPE), stomatitis or haematological toxicity, the dose may be reduced or delayed. Guidelines for SOPILCIN dose modification secondary to these adverse events 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 (**TABLE 3**) provides the schedule followed for dose modification in clinical trials in the treatment of patients with breast or ovarian cancer only.

Dose modification in patients with AIDS-KS is addressed in section 4.8.

TABLE 1: PALMAR-PLANTAR ERYTHRODYSAESTHESIA
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	Week after prior SOPILCIN dose		
Toxicity Grade After Prior SOPILCIN 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 for an additional week	Re-dose unless patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait for 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	Wait an additional week	Wait an additional week	Withdraw patient

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walking or normal daily activities; cannot wear regular clothing)			
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 SOPILCIN dose		
Toxicity Grade After Prior SOPILCIN 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 an	Re-dose unless patient has experienced a previous Grade 3 or 4 stomatitis, in which case wait an	Decrease dose by 25 %; return to 4-week interval or withdraw patient per medical

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	additional week	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 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 (ANC OR PLATELETS) – MANAGEMENT OF PATIENTS WITH BREAST OR OVARIAN CANCER

GRADE	ANC	PLATELETS	MODIFICATION
1	1 500 – 1 900	75 000 – 150 000	Resume treatment with no dose reduction
2	1 000 - < 1 500	50 000 - < 75 000	Wait until ANC ≥ 1 500 and platelets ≥ 75 000; re-dose with no dose reduction
3	500 - < 1 000	25 000 - < 50 000	Wait until ANC ≥ 1 500 and platelets ≥ 75 000

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			75 000; re-dose with no dose reduction
4	< 500	< 25 000	Wait until ANC \geq 1 500 and platelets \geq 75 000; decrease dose by 25 % or continue full dose with growth factor support

For multiple myeloma patients treated with SOPILCIN in combination with bortezomib who experience PPE or stomatitis, the SOPILCIN dose should be modified as described in the **TABLES 1 and 2** above respectively. For more detailed information on bortezomib dosing and dosage adjustments, refer to the Professional Information for bortezomib.

TABLE 4: DOSAGE ADJUSTMENTS FOR SOPILCIN + BORTEZOMIB COMBINATION THERAPY

PATIENTS WITH MULTIPLE MYELOMA

Patient Status	SOPILCIN	Bortezomib
Fever \geq 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-	Do not dose until recovered	Do not dose until recovered

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haematologic medicine related toxicity	to Grade < 2 and reduce dose by 25 % for all subsequent doses	to Grade < 2 and reduce dose by 25 % for all subsequent doses
Neuropathic pain or peripheral neuropathy	No dosage adjustments	Refer to the Professional Information 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:

SOPILCIN pharmacokinetics determined in a small number of patients with elevated total bilirubin levels do not differ from patients with normal total bilirubin; however; until further experience is gained, the SOPILCIN dosage in patients with impaired hepatic function should be reduced based on the experience obtained from breast and ovarian clinical trial programs as follows: At initiation of therapy, if the bilirubin is between 1,2 to 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. SOPILCIN can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 times the upper limit of the normal range. Prior to SOPILCIN administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase and bilirubin.

Patients with impaired renal function:

As doxorubicin is metabolised by the liver and excreted in the bile, dose modification should not be required with SOPILCIN. Population-based analysis confirms that changes in the renal function over the range tested (estimated creatinine clearance 30 to 156

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ml/min) do not alter the pharmacokinetics of SOPILCIN. No pharmacokinetic data are available for patients with creatinine clearance of less than 30 ml/min.

AIDS-KS patients with splenectomy:

Since there is no experience with SOPILCIN in patients with splenectomy, treatment with SOPILCIN not recommended.

Elderly patients:

Population-based analysis demonstrates that age across the range tested (21 to 75 years) does not significantly alter the pharmacokinetics of SOPILCIN.

Paediatric population

The safety and efficacy of SOPILCIN in patients less than 18 years of age has not been established.

Method of administration

SOPILCIN is administered as an intravenous infusion. For further instructions on preparation and special precautions for handling see section 6.6.

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

Breast cancer/ Ovarian cancer:

For doses < 90 mg: Dilute SOPILCIN in 250 ml Dextrose 5 % in Water.

For doses ≥ 90 mg: Dilute SOPILCIN in 500 ml Dextrose 5 % in Water.

To minimise the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent SOPILCIN infusions may be administered over a 60-minute period.

In those patients who experienced an infusion reaction, 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 reaction the infusion rate may then be doubled for the next 15

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minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

Multiple myeloma:

For doses < 90 mg: Dilute SOPILCIN in 250 ml of 5 % (50 mg/ml) glucose solution for infusion.

For doses ≥ 90 mg: Dilute SOPILCIN in 500 ml of 5 % (50 mg/ml) glucose solution for infusion.

The intravenous catheter and tubing should be flushed with 5 % glucose for infusion between administration of the 2 medicines. The first infusion of SOPILCIN should be administered over 90 minutes as follows:

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

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

- 10 ml over first 10 minutes
- 20 ml over next 10 minutes
- 40 ml over 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.

AIDS-KS patients:

SOPILCIN diluted in 250 ml Dextrose 5 % in Water is administered by intravenous infusion over 30 minutes.

4.3 Contraindications

SOPILCIN is contra-indicated in patients who have a history of hypersensitivity reactions to doxorubicin HCl, peanut or soya, or to any of the excipients listed in section 6.1.

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SOPILCIN should not be administered during pregnancy or while breast-feeding.

SOPILCIN must not be used to treat AIDS-related KS that may be treated effectively with local therapy or systemic alpha-interferon.

The safety and effectiveness in patients less than 18 years of age have not been established.

4.4 Special warnings and precautions for use

Given the difference in dosing schedules and pharmacokinetic profiles, SOPILCIN should not be used interchangeably with other formulations of doxorubicin hydrochloride (see section 4.2 and 5.2).

Cardiac risk:

All patients receiving SOPILCIN should routinely undergo frequent electrocardiogram (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 SOPILCIN therapy.

However, reduction of the QRS complex is considered more indicative of cardiac toxicity.

If this change occurs, the most definitive test for SOPILCIN 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 a 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 SOPILCIN therapy and should be repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional administration of SOPILCIN that exceeds a lifetime cumulative anthracycline dose of 450 mg/m².

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 a prognostically relevant value (e.g., < 45 %),

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endomyocardial biopsies should be performed and the benefit of continued therapy with SOPILCIN 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 mentioned above concerning the monitoring of cardiac performance during SOPILCIN 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 SOPILCIN 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 SOPILCIN only when the benefit outweighs the risk to the patient.

Exercise caution in patients with impaired cardiac function who receive SOPILCIN.

Caution should be observed in patients who have received other anthracyclines. The total dose of doxorubicin HCl 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/m² in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide therapy.

The cardiac safety profile for the dosing schedule recommended for both breast and ovarian cancer (50 mg/m²) is similar to the 20 mg/m² profile in patients with AIDS-KS (see section 4.8).

Myelosuppression:

Many patients treated with SOPILCIN have baseline myelosuppression due to such factors as their pre-existing HIV disease or numerous concomitants or previous medications, or tumours involving bone marrow.

In the pivotal trial in patients with ovarian cancer treated at a dose of 50 mg/m², myelosuppression was generally mild to moderate, reversible, and was not associated with

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episodes of neutropenic infection or sepsis.

In contrast to the experience in patients with breast cancer or ovarian cancer, 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 must be performed frequently during the course of SOPILCIN therapy, and at a minimum, prior to each dose of SOPILCIN.

Persistent severe myelosuppression, although not seen in patients with ovarian cancer, may result in haemorrhage or super-infection.

In controlled clinical studies in patients with AIDS-KS against a bleomycin/vincristine regimen, opportunistic infections were apparently more frequent during treatment with doxorubicin. Patients and doctors must be aware of this higher incidence and take action as appropriate.

Secondary haematological malignancies:

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

Secondary oral neoplasms:

Cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to SOPILCIN or those receiving a cumulative SOPILCIN dose greater than 720 mg/m². Cases of secondary oral cancer were diagnosed both, during treatment with SOPILCIN, 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 reactions 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

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and/or hypotension may occur within minutes of starting the infusion of SOPILCIN (see section 4.8).

Convulsions also have been observed in relation to infusion reactions (see section 4.8). 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 occur 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 (see section 4.2).

Diabetic patients:

Please note that each vial of SOPILCIN contains sucrose and is administered in Dextrose 5 % in Water for intravenous infusion. An adjustment to the treatment of diabetes may be required.

Other

Combination therapy with SOPILCIN has been extensively studied in solid tumour populations. However, the efficacy of SOPILCIN combination chemotherapy has not been established in the treatment of ovarian cancer.

For common adverse events which required dose modification or discontinuation see section 4.8.

4.5 Interaction with other medicines and other forms of interaction

No formal medicine interaction studies have been performed with doxorubicin, although phase II combination trials with conventional chemotherapy medicines have been conducted in patients with gynaecological malignancies. Exercise caution in the concomitant use of medicines known to interact with standard doxorubicin hydrochloride. SOPILCIN, like other doxorubicin hydrochloride preparations, may potentiate the toxicity of other anti-cancer therapies. During clinical trials in patients with solid tumours (including breast and ovarian cancer) who have received

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concomitant cyclophosphamide or taxanes, no new additive toxicities were noted.

In patients with AIDS, exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with standard doxorubicin hydrochloride. Caution must be exercised when giving any other cytotoxic medicines, especially myelotoxic medicines, at the same time.

4.6 Fertility, pregnancy and lactation

Pregnancy

Doxorubicin HCl is teratogenic in animals. There is no experience in pregnant women with SOPILCIN. Teratogenicity cannot be ruled out. Doxorubicin hydrochloride is suspected to cause serious birth defects when administered during pregnancy.

Therefore, SOPILCIN should not be administered during pregnancy (see section 4.3).

Women of child-bearing potential

Women of child-bearing potential must be advised to avoid pregnancy while they or their male partner are receiving SOPILCIN and in the six months following discontinuation of SOPILCIN therapy.

Breast-feeding

It is not known whether doxorubicin is excreted in human milk.

Because many medicines, including anthracyclines, are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, mothers must discontinue nursing prior to beginning SOPILCIN treatment (see section 4.3).

Fertility

The effect of doxorubicin hydrochloride on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

Doxorubicin HCl has no or negligible influence on the ability to drive and use machines.

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However, dizziness and somnolence have been associated infrequently with the administration of Doxorubicin HCl (see section 4.8). Patients who suffer from these effects must avoid driving and operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most common undesirable effect reported in breast/ovarian clinical trials (50 mg/m² every 4 weeks) was palmar-plantar erythrodysesthesia (PPE). The overall incidence of PPE reported was 44,0 %-46,1 %. These effects were mostly mild, with severe (grade 3) cases reported in 17 %-19,5 %. The reported incidence of life-threatening (grade 4) cases was < 1%. PPE infrequently resulted in permanent treatment discontinuation (3,7 %-7,0 %). PPE is characterised by painful, macular reddening skin eruptions. In patients experiencing this event, it is generally seen after two or three cycles of treatment. Improvement usually occurs in one - two weeks, and in some cases, may take up to 4 weeks or longer for complete resolution. Pyridoxine at a dose of 50-150 mg per day and corticosteroids have been used for the prophylaxis and treatment of PPE, however, these therapies have not been evaluated in phase III trials. Other strategies to prevent and treat PPE include keeping hands and feet cool, by exposing them to cool 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 primarily related to the dose schedule and can be reduced by extending the dose interval 1-2 weeks (see section 4.2). However, this reaction can be severe and debilitating in some patients and may require discontinuation of treatment. Stomatitis/mucositis and nausea were also commonly reported in breast/ovarian cancer patient populations, whereas in the AIDS-KS Program (20 mg/m² every 2 weeks), myelosuppression (mostly leukopaenia) was the most common side effect (see AIDS-KS). 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 most frequently reported (medicine-related treatment-

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emergent) adverse events in combination therapy (doxorubicin HCl+ bortezomib) were nausea (40 %), diarrhoea (35 %), neutropaenia (33 %), thrombocytopenia (29 %), vomiting (28 %), fatigue (27 %), and constipation (22 %).

Breast cancer program

509 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with doxorubicin HCl at a dose of 50 mg/m² every 4 weeks, or doxorubicin at a dose of 60 mg/m² every 3 weeks, in a phase III clinical trial. The following common adverse events were reported more often with doxorubicin at a dose of 60 mg/m² every 3 weeks than with doxorubicin HCl at a dose of 50 mg/m² every 4 weeks: nausea, vomiting, alopecia and neutropaenia.

Mucositis, and stomatitis were reported more commonly with doxorubicin HCl at a dose of 50 mg/m² every 4 weeks than with doxorubicin at a dose of 60 mg/m² every 3 weeks. The average duration of the most common severe (grade 3/4) events for both groups was 30 days or less. See **TABLE 5** for complete listing of undesirable effects reported in doxorubicin patients - treated with a dose of 50 mg/m² every 4 weeks.

The incidence of life threatening (grade 4) haematologic effects was < 1,0 % and sepsis was reported in 1 % of patients. Growth factor support or transfusion support was necessary in 5,1 % and 5,5 % of patients, respectively (see section 4.2).

Clinically significant laboratory abnormalities (grades 3 and 4) was low with elevated total bilirubin, AST and ALT reported in 2,4 %, 1,6 % and < 1 % of patients respectively.

No clinically significant increases in serum creatinine were reported.

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TABLE 5: Treatment related undesirable effects reported in breast cancer clinical trials (50 mg/m² every 4 weeks)

CIOMS III

AE by body system	Breast cancer All severities	Breast cancer Grades 3/4	Breast cancer
Infections and infestations			

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Frequent	Pharyngitis		Folliculitis, fungal infection, cold sores (non-herpetic), upper respiratory tract infection
Less frequent		Pharyngitis	
Blood and lymphatic system disorders			
Frequent	Leukopaenia, anaemia, neutropaenia, thrombocytopaenia	Leukopaenia, anaemia	Thrombocythemia
Less frequent		Neutropaenia	
Metabolism and nutrition disorders			
Frequent	Anorexia		
		Anorexia	
Nervous system disorders			
Frequent	Paresthesia	Paresthesia	Peripheral neuropathy
Less frequent	Somnolence		
Eye disorders			
Frequent			Lacrimation, blurred vision
Cardiac disorders			
Frequent			Ventricular arrhythmia
Respiratory, thoracic and mediastinal disorders			
Frequent			Epistaxis
Gastrointestinal disorders			
Frequent	Nausea, stomatitis, vomiting, abdominal pain, constipation, diarrhoea, dyspepsia, mouth ulceration	Abdominal pain, diarrhoea, nausea, stomatitis	Oral pain
Less frequent		Mouth ulceration, constipation, vomiting	
Skin and subcutaneous tissue disorders			
Frequent	PPE*, alopecia, rash, dry skin, skin discolouration, abnormal pigmentation, erythema	PPE*, rash	Bullous eruption, dermatitis, erythematous rash, nail disorder, scaly skin
Less frequent		Abnormal pigmentation, erythema	
Musculoskeletal and connective tissue disorders			

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Frequent			Leg cramps, bone pain, musculoskeletal pain
Reproductive system and breast disorders			
Frequent			Breast pain
General disorders and administration site conditions			
Frequent	Asthenia, fatigue, mucositis NOS, weakness, fever, pain	Asthenia, mucositis NOS	Oedema, leg oedema
Less frequent		Fatigue, weakness, pain	

* palmar-plantar erythrodysesthesia (Hand-foot syndrome).

Ovarian cancer program

512 patients with ovarian cancer (a subset of 876 solid tumour patients) were treated with doxorubicin at a dose of 50 mg/m² in clinical trials. See **TABLE 6** for undesirable effects reported in doxorubicin-treated patients.

TABLE 6: Treatment related undesirable effects reported in ovarian cancer clinical trials (50 mg/m² every 4 weeks)

CIOMS III

AE by body system	Ovarian cancer All severities	Ovarian cancer Grades 3/4	Ovarian cancer
Infections and infestations			
Frequent	Pharyngitis		Infection, oral moniliasis, herpes zoster, urinary tract infection
Less frequent		Pharyngitis	
Blood and lymphatic system disorders			
Frequent	Leukopaenia, anaemia, neutropaenia, thrombocytopaenia	Neutropaenia, leukopaenia, anaemia, thrombocytopaenia	Hypochromic anaemia
Immune system disorders			
Frequent			Allergic reaction
Metabolism and nutrition disorders			
Frequent	Anorexia		Dehydration, cachexia
Less frequent		Anorexia	

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Psychiatric disorders			
Frequent			Anxiety, depression, insomnia
Nervous system disorders			
Frequent	Paresthesia, somnolence		Headache, dizziness, neuropathy, hypertonia
Less frequent		Paresthesia, somnolence	
Eye disorders			
Frequent			Conjunctivitis
Cardiac disorders			
Frequent			Cardiovascular disorder
Vascular disorders			
Frequent			Vasodilatation
Respiratory, thoracic and mediastinal disorders			
Frequent			Dyspnoea, increased cough
Gastrointestinal disorders			
Frequent	Constipation, diarrhoea, nausea, stomatitis, vomiting, abdominal pain, dyspepsia, mouth ulceration	Nausea, stomatitis, vomiting, abdominal pain, diarrhoea	Mouth ulceration, esophagitis, nausea and vomiting, gastritis, dysphagia, dry mouth, flatulence, gingivitis, taste perversion
Less frequent		Constipation, dyspepsia, mouth ulceration	
Skin and subcutaneous tissue disorders			
Frequent	PPE*, alopecia, rash, dry skin, skin discolouration	PPE*, alopecia, rash	Vesiculobullous rash, pruritus, exfoliative dermatitis, skin disorder, maculopapular rash, sweating, acne, skin ulcer
Musculoskeletal and connective tissue disorders			
Frequent			Back pain, myalgia

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Renal and urinary disorders			
Frequent			Dysuria
Reproductive system and breast disorders			
Frequent			Vaginitis
General disorders and administration site conditions			
Frequent	Asthenia, mucous membrane disorder, fever, pain	Asthenia, mucous membrane disorder, pain	Chills, chest pain, malaise, peripheral oedema
Less frequent		Fever	
Investigations			
Frequent			Weight loss

* palmar-plantar erythrodysesthesia (Hand-foot syndrome).

Myelosuppression was mostly mild or moderate and manageable. Sepsis related to leukopaenia was observed infrequently (< 1 %). Growth factor support was required infrequently (< 5 %) and transfusion support was required in approximately 15 % of patients (see section 4.2).

In a subset of 410 patients with ovarian cancer, clinically significant laboratory abnormalities occurring in clinical trials with doxorubicin included increases in total bilirubin (usually in patients with liver metastases) (5 %) and serum creatinine levels (5 %).

Increases in AST were less frequently (< 1 %) reported.

Solid tumour patients: in a larger cohort of 929 patients with solid tumours (including breast cancer and ovarian cancer) predominantly treated at a dose of 50 mg/m² every 4 weeks, the safety profile and incidence of adverse effects were comparable to those of the patients treated in the pivotal breast cancer and ovarian cancer trials.

Multiple myeloma program

318 patients were treated with combination therapy of doxorubicin 30 mg/m² and bortezomib or with bortezomib monotherapy (328 patients) in a phase III clinical trial.

TABLE 7 includes adverse effects reported in ≥ 5 % patients treated with combination therapy of doxorubicin plus bortezomib.

Neutropaenia, thrombocytopaenia, and anaemia were the most frequently reported haematologic events reported with both combination therapy of doxorubicin plus

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bortezomib and bortezomib monotherapy. The incidence of grade 3 and 4 neutropaenia and thrombocytopaenia was higher in the combination therapy group than in the monotherapy group. The incidence of anaemia was similar in both treatment groups. Stomatitis was reported more frequently in the combination therapy group (16 %) than in the monotherapy group (3 %), and most cases were grade 2 or less in severity. Grade 3 stomatitis was reported in 2 % of patients in the combination therapy group. No grade 4 stomatitis was reported.

Nausea and vomiting were reported more frequently in the combination therapy group and were mostly grade 1 and 2 in severity.

Treatment discontinuation of one or both medicines due to adverse events was seen in 38 % of patients. Common adverse events which led to treatment discontinuation of bortezomib and doxorubicin included PPE, neuralgia, peripheral neuropathy, peripheral sensory neuropathy, thrombocytopaenia, decreased ejection fraction, and fatigue.

TABLE 7: Treatment related undesirable effects reported in multiple myeloma clinical trial (doxorubicin 30 mg/m² in combination with bortezomib every 3 weeks) by severity

CIOMS III

AE by body system	All Severities	Grades 3/4**	All Severities
Infections and infestations			
Frequent	Herpes simplex, herpes zoster	Herpes zoster	Pneumonia, nasopharyngitis, upper respiratory tract infection, oral candidiasis
Blood and lymphatic system disorders			
Frequent	Anaemia, neutropaenia, thrombocytopaenia, leukopaenia	Neutropaenia, thrombocytopaenia, anaemia, leukopaenia	Febrile neutropaenia, lymphopaenia
Metabolism and nutrition disorders			
Frequent	Anorexia, decreased appetite	Anorexia	Dehydration, hypokalaemia, hyperkalaemia, hypomagnesaemia, hyponatraemia, hypocalcaemia

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Less frequent		Decreased appetite	
Psychiatric disorders			
Frequent	Insomnia		Anxiety
Nervous system disorders			
Frequent	Peripheral sensory neuropathy, neuralgia, headache, neuropathy peripheral, paraesthesia, polyneuropathy, dizziness, dysgeusia	Neuralgia, peripheral neuropathy, neuropathy	Lethargy, hypoaesthesia, syncope, dysaesthesia
Less frequent		Headache, peripheral sensory neuropathy, paraesthesia, dizziness	
Eye disorders			
Frequent			Conjunctivitis
Vascular disorders			
Frequent			Hypotension, orthostatic hypotension, flushing, hypertension, phlebitis
Respiratory, thoracic and mediastinal disorders			
Frequent	Dyspnoea		Cough, epistaxis exertional dyspnoea
Less frequent		Dyspnoea	
Gastrointestinal disorders			
Frequent	Nausea, diarrhoea, vomiting, constipation, stomatitis, abdominal pain, dyspepsia	Nausea, diarrhoea, vomiting, stomatitis	Upper abdominal pain, mouth ulceration, dry mouth, dysphagia, aphthous stomatitis
Less frequent		Constipation, abdominal pain, dyspepsia	
Skin and subcutaneous tissue disorders			
Frequent	PPE*, rash, dry skin	PPE*	Pruritus, papular rash, allergic dermatitis, erythema, skin

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			hyperpigmentation, petechiae, alopecia, medicine eruption
Frequent		Rash	
Musculoskeletal and connective tissue disorders			
Frequent	Pain in extremity		Arthralgia, myalgia, muscle spasms, muscular weakness, musculoskeletal pain, musculoskeletal chest pain
Reproductive system and breast disorders			
Frequent			Scrotal erythema
General disorders and administration site conditions			
Frequent	Asthenia, fatigue, pyrexia	Asthenia, fatigue	Peripheral oedema, chills, influenza-like illness, malaise, hyperthermia
Frequent		Pyrexia	
Investigations			
Frequent	Weight decreased		Increased aspartate aminotransferase, decreased ejection fraction, increased blood creatinine, increased alanine aminotransferase

* Palmar-plantar erythrodysesthesia (Hand-foot syndrome).

** Grade 3/4 adverse events are based on the adverse event terms of all severities with an overall incidence $\geq 5\%$ (see adverse events listed in first column).

AIDS-related KS program

Clinical studies on AIDS-KS patients treated at 20 mg/m² with doxorubicin show that myelosuppression was the most frequent undesirable effect considered related to doxorubicin occurring very commonly (in approximately one-half of the patients).

Leukopaenia was the most frequent undesirable effect experienced with doxorubicin.

Neutropaenia, anaemia and thrombocytopaenia have been observed. These effects may occur early on in treatment. Haematological toxicity may require dose reduction or

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suspension or delay of therapy. Temporarily suspend doxorubicin treatment in patients when the ANC count is < 1,000/mm³ and/or the platelet count is < 50,000/mm³. G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is < 1,000/mm³ in subsequent cycles. The haematological toxicity for ovarian cancer patients was less severe than in the AIDS-KS setting (see section for ovarian cancer patients above).

Respiratory effects commonly 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 carinii* pneumonia, and mycobacterium avium complex.

TABLE 8: Undesirable effects observed in patients with AIDS-related KS according to CIOMS III frequency categories

Infections and infestations	
Frequent	oral moniliasis
Blood and lymphatic system disorders	
Frequent	neutropaenia, anaemia, leukopaenia thrombocytopaenia
Metabolism and nutrition disorders	
Frequent	anorexia
Psychiatric disorders	
Less frequent	confusion
Nervous system disorders	
Frequent	dizziness
Less frequent	paresthesia
Eye disorders	
Frequent	retinitis
Vascular disorders	
Frequent	vasodilatation
Respiratory, thoracic and mediastinal disorders	
Frequent	dyspnoea
Gastrointestinal disorders	

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Frequent	nausea, diarrhoea, stomatitis, vomiting, mouth ulceration, abdominal pain, glossitis, constipation, nausea and vomiting
Skin and subcutaneous tissue disorders	
Frequent	alopecia, rash
Less frequent	palmar-plantar erythrodysesthesia (PPE)
General disorders and administration site conditions	
Frequent	asthenia, fever, infusion-associated acute reactions
Investigations	
Frequent	weight loss

Other less frequently (< 5 %) observed undesirable effects included hypersensitivity reactions including anaphylactic reactions. Following marketing, bullous eruption has been reported rarely in this population.

Clinically significant laboratory abnormalities frequently (≥ 5 %) occurred including increases in alkaline phosphatase; AST and bilirubin which were believed to be related to the underlying disease and not doxorubicin. Reduction in haemoglobin and platelets were less frequently (< 5 %) reported. Sepsis related to leukopaenia was rarely (< 1 %) observed. Some of these abnormalities may have been related to the underlying HIV infection and not doxorubicin.

All patients

100 out of 929 patients (10,8 %) with solid tumours were described as having an infusion-associated reaction during treatment with doxorubicin as defined by the following Costart terms: allergic reaction, anaphylactoid reaction, asthma, face oedema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnoea, pharyngitis, rash, pruritus, sweating, injection site reaction and medicinal product interaction. Permanent treatment discontinuation was infrequently reported at 2 %. A similar incidence of infusion reactions (12,4 %) and treatment discontinuation (1,5 %) was observed in the breast cancer program. In patients with multiple myeloma receiving doxorubicin plus bortezomib, infusion-associated

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reactions have been reported at a rate of 3 %. In patients with AIDS-KS, infusion-associated reactions, were characterised by flushing, shortness of breath, facial oedema, headache, chills, back pain, tightness in the chest and throat and/or hypotension and can be expected at the rate of 5 % to 10 %. Very rarely, convulsions have been observed in relation to infusion reactions. In all patients, infusion-associated reactions occurred primarily during the first infusion. Temporarily stopping the infusion usually resolves these symptoms without further therapy. In nearly all patients, doxorubicin treatment can be resumed after all symptoms have resolved without recurrence. Infusion reactions rarely recur after the first treatment cycle with doxorubicin (see section 4.2).

Myelosuppression associated with anaemia, thrombocytopaenia, leukopaenia, and rarely febrile neutropaenia, has been reported in doxorubicin-treated patients.

Stomatitis has been reported in patients receiving continuous infusions of conventional doxorubicin hydrochloride and was frequently reported in patients receiving doxorubicin. It did not interfere with patients completing therapy and no dosage adjustments are generally required, unless stomatitis is affecting a patient's ability to eat. In this case, the dose interval may be extended by 1-2 weeks or the dose reduced (see section 4.2).

An increased incidence of congestive heart failure is associated with doxorubicin therapy

at cumulative lifetime doses > 450 mg/m² or at lower doses for patients with cardiac risk factors. Endomyocardial biopsies on nine of ten AIDS-KS patients that received cumulative doses of doxorubicin greater than 460 mg/m² indicated no evidence of anthracycline-induced cardiomyopathy. The recommended dose of doxorubicin for AIDS-KS patients is 20 mg/m² every two-to-three weeks. The cumulative dose at which cardiotoxicity would become a concern for these AIDS-KS patients (> 400 mg/m²) 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/m²-1,680 mg/m². The range of Billingham cardiotoxicity scores was grades 0-1,5. These grading scores are consistent with no or

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mild cardiac toxicity.

In a pivotal phase III trial, 58/509 (11,4 %) randomised subjects (10 treated with doxorubicin at a dose of 50 mg/m²/every 4 weeks versus 48 treated with doxorubicin at a dose of 60 mg/m²/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 dosed at 50 mg/m² who had cardiac toxicity by LVEF criteria developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin subjects dosed at 60 mg/m² who had cardiac toxicity by LVEF criteria 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 50 mg/m²/cycle with lifetime cumulative anthracycline doses up to 1,532 mg/m², the incidence of clinically significant cardiac dysfunction was low. Of the 418 patients treated with doxorubicin 50 mg/m²/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/m², 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/m²), discontinued study treatment because of clinical symptoms of congestive heart failure.

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

Although local necrosis following extravasation has been reported very rarely, Doxorubicin

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

Recall of skin reaction due to prior radiotherapy has rarely occurred with Doxorubicin administration.

Post-marketing experience

Adverse drug reactions identified during the post-marketing experience with doxorubicin are described in **TABLE 9**. The frequencies are provided according to the following convention:

TABLE 9: Adverse drug reactions identified during the post-marketing experience with doxorubicin

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Less frequent	secondary oral neoplasms ¹
Vascular disorders	
Less frequent	venous thromboembolism, including thrombophlebitis, venous thrombosis and pulmonary embolism
Skin and subcutaneous tissue disorders	
Less frequent	erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis

¹ Cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to doxorubicin or those receiving a cumulative doxorubicin dose greater than 720 mg/m² (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important.

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Health care 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 sections 4.4 and 4.8.

Acute overdosage with doxorubicin HCl worsens the toxic effects of mucositis, leukopaenia and thrombocytopaenia. 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 Cytostatics

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances),

ATC code: L01DB01

Mechanism of action

The active ingredient of SOPILCIN is doxorubicin hydrochloride. The exact mechanism of the anti-tumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effects.

This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix, thus preventing their unwinding for replication.

5.2 Pharmacokinetic properties

SOPILCIN is a long-circulating pegylated liposomal formulation of doxorubicin hydrochloride. Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface creating a protective coating that reduces

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interactions between the lipid bilayer membrane and the plasma components. This allows the doxorubicin liposomes to circulate for prolonged periods in the blood stream. Pegylated liposomes are small enough (average diameter of approximately 100 nm) to pass intact (extravasate) through defective blood vessels supplying tumours. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumours has been seen in mice with C-26 colon carcinoma tumours and in transgenic mice with KS-like lesions. The pegylated liposomes also have a low permeability lipid matrix and internal aqueous buffer system that combine to keep doxorubicin hydrochloride encapsulated during liposome residence time in circulation.

The plasma pharmacokinetics of doxorubicin in humans differ significantly from those reported in the literature for standard doxorubicin hydrochloride preparations. At lower doses (10 mg/m²–20 mg/m²) doxorubicin displayed linear pharmacokinetics. Over the dose range of 10 mg/m²–60 mg/m² doxorubicin displayed non-linear pharmacokinetics. Standard doxorubicin hydrochloride displays extensive tissue distribution (volume of distribution: 700 to 1,100 l/m²) and a rapid elimination clearance (24 to 73 l/h/m²). In contrast, the pharmacokinetic profile of doxorubicin indicates that doxorubicin is confined mostly to the vascular fluid volume and that the clearance of doxorubicin from the blood is dependent upon the liposomal carrier. Doxorubicin becomes available after the liposomes are extravasated and enter the tissue compartment.

At equivalent doses, the plasma concentration and AUC values of doxorubicin which represent mostly pegylated liposomal doxorubicin hydrochloride (containing 90 % to 95 % of the measured doxorubicin) are significantly higher than those achieved with standard doxorubicin hydrochloride preparations.

Doxorubicin should not be used interchangeably with other formulations of doxorubicin hydrochloride.

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Breast cancer patients:

The pharmacokinetics of doxorubicin determined in 18 patients with breast carcinoma were similar to the pharmacokinetics determined in a larger population of 120 patients with various cancers. The mean intrinsic clearance was 0,016 l/h/m² (range 0,008-0,027 l/h/m²), the mean central volume of distribution was 1,46 l/m² (range 1,10-1,64 l/m²). The mean apparent half-life was 71,5 hours (range 45,2-98,5 hours).

Ovarian cancer patients:

The pharmacokinetics of doxorubicin at higher doses is non-linear and exposure is expected to be longer than at lower doses. At 50 mg/m² in patients with ovarian carcinoma, the mean intrinsic clearance was 0,021 l/h/m² (range 0,009 to 0,041 l/h/m²), the mean central volume of distribution was 1,95 l/m² (range 1,67 to 2,40 l/m²). The mean apparent half-life was 75,0 hours (range 36,1 to 125 hours).

Doxorubicin displayed linear pharmacokinetics in the dose range 10 to 20 mg/m².

Disposition occurred in two phases after doxorubicin administration, 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 Patients:

The plasma pharmacokinetics of doxorubicin were evaluated in 23 patients with Kaposi's Sarcoma (KS) who received single doses of 20 mg/m² administered by a 30-minute infusion.

The pharmacokinetic parameters of doxorubicin (primarily representing pegylated liposomal doxorubicin HCl and low levels of unencapsulated doxorubicin HCl) observed after the 20 mg/m² doses are presented in **TABLE 10**.

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TABLE 10: Pharmacokinetic parameters in doxorubicin-treated AIDS-KS patients	
	Mean ± Standard Error
Parameter	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 (mcg/ml.h)	590 ± 58,7
λ ₁ half-life (hours)	5,2 ± 1,4
λ ₂ half-life (hours)	55,0 ± 4,8

* Measured at the end of a 30-minute infusion.

5.3 Preclinical safety data

In repeat dose studies conducted in animals, the toxicity profile of doxorubicin appears very similar to that reported in humans who receive long-term infusions of standard doxorubicin hydrochloride. With doxorubicin, the encapsulation of doxorubicin hydrochloride in pegylated liposomes results in the effects having a differing strength, as follows.

Cardiotoxicity

Studies in rabbits have shown that the cardiotoxicity of doxorubicin is reduced compared with conventional doxorubicin hydrochloride preparations.

Dermal toxicity

In studies performed after the repeated administration of doxorubicin to rats and dogs, serious dermal inflammations and ulcer formations were observed at clinically relevant dosages. In the study in dogs, the occurrence and severity of these lesions was reduced by lowering the dose or prolonging the intervals between doses. Similar dermal lesions, which are described as palmar-plantar erythrodysesthesia were also observed in patients after long-term intravenous infusion (see section 4.8).

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Anaphylactoid response

During repeat dose toxicology studies in dogs, an acute response characterised by hypotension, pale mucous membranes, salivation, emesis and periods of hyperactivity followed by hypoactivity and lethargy was observed following administration of pegylated liposomes (placebo). A similar, but less severe response was also noted in dogs treated with doxorubicin and standard doxorubicin.

The hypotensive response was reduced in magnitude by pretreatment with antihistamines. However, the response was not life-threatening and the dogs recovered quickly upon discontinuation of treatment.

Local toxicity

Subcutaneous tolerance studies indicate that doxorubicin, as against standard doxorubicin hydrochloride, causes slighter local irritation or damage to the tissue after a possible extravasation.

Mutagenicity and carcinogenicity

Although no studies have been conducted with doxorubicin, doxorubicin hydrochloride, the pharmacologically active ingredient of doxorubicin, is mutagenic and carcinogenic. Pegylated placebo liposomes are neither mutagenic nor genotoxic.

Reproductive toxicity

Doxorubicin resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg. Decreased testicular weights and hypospermia were present in rats after repeat doses $\geq 0,25$ mg/kg/day and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (see section 4.6).

Nephrotoxicity

A study has shown that doxorubicin at a single intravenous dose of over twice the clinical dose produces renal toxicity in monkeys. Renal toxicity has been observed with even lower single doses of doxorubicin HCl in rats and rabbits. Since an evaluation of the post-marketing safety database for doxorubicin in patients has not suggested a significant

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nephrotoxicity liability of doxorubicin, these findings in monkeys may not have relevance to patient risk assessment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N-(carbamoyl-methoxypolyethylene glycol 2000)-

1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)

fully hydrogenated soy phosphatidylcholine (HSPC)

ammonium sulfate

cholesterol

histidine

sucrose

water for injection

hydrochloric acid (for pH-adjustment)

sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

18 months.

After dilution:

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C.

- From a microbiological point of view, the product should be used immediately. If not used

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immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 °C to 8 °C.

- Partially used vials must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze. Store in the original package in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

SOPILCIN 20 mg/10 ml: Carton containing a single use, Type 1 clear glass vial closed with a bromobutyl rubber stopper and sealed with an aluminium seal / dark blue plastic flip-off cap.

SOPILCIN 50 mg/25 ml: Carton containing a single use, Type 1 clear glass vial closed with a bromobutyl rubber stopper and sealed with an aluminium seal / red plastic flip-off cap.

Each 10 ml vial or 25 ml vial of SOPILCIN contains doxorubicin hydrochloride 2 mg/ml.

SOPILCIN is supplied as a single vial in a pack or 10 vials in a pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Caution should be exercised in handling SOPILCIN solution. The use of gloves is required.

If SOPILCIN comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. SOPILCIN should be handled and disposed of in a manner consistent with that of other anticancer medicines.

Determine the dose of SOPILCIN to be administered (based upon the recommended dose and the patient's body surface area). Take the appropriate volume of SOPILCIN up into a

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sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in SOPILCIN.

The appropriate dose of SOPILCIN must be diluted in Dextrose 5 % in Water prior to administration. For doses < 90 mg, dilute SOPILCIN in 250 ml, and for doses ≥ 90 mg, dilute SOPILCIN in 500 ml of Dextrose 5 % in Water.

The use of any diluent other than Dextrose 5 % in Water for Infusion, or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of SOPILCIN. It is recommended that the SOPILCIN 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 in-line filters.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER(S)

SOPILCIN 20 mg/10 ml: 51/26/0265

SOPILCIN 50 mg/25 ml: 51/26/0266

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 March 2021

**APPROVED PROFESSIONAL INFORMATION:
DR. REDDY'S LABORATORIES (PTY) LTD.
SOPILCIN 20 mg/10 ml & 50 mg/25 ml
(SOLUTION FOR INFUSION)**

10 DATE OF REVISION OF THE TEXT

01 August 2021