**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

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.

Excipients with known effect :

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

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.

The suspension is translucent and red.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

SOPILCIN is indicated:

**Breast cancer:**

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.

**Ovarian cancer:**

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

**Multiple myeloma:**

- 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):**

- In patients with low $CD_4$ counts (< 200 $CD_4$ lymphocytes/$mm^3$) and extensive mucocutaneous or visceral disease.

### 4.2 Posology and method of administration

**Posology**

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).

***Breast cancer or Ovarian cancer:***

SOPILCIN is administered intravenously at a dose of 50 mg/$m^2$ once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

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

***Multiple myeloma:***

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

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 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 SOPILCIN 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 SOPILCIN will be administered over 1 hour, as tolerated. If an infusion reaction to SOPILCIN occurs, stop the infusion. After the symptoms have resolved, attempt to administer remaining SOPILCIN 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.

***AIDS-KS patients:***

SOPILCIN should be administered intravenously at 20 mg/m$^2$ 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.

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

***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 erythrodysaesthesia (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** | | | |
|---|---|---|---|
| | **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 walking or normal daily activities; cannot wear regular clothing) | Wait an additional week | Wait an additional week | Withdraw patient |
| **Grade 4** (diffuse or local process causing infectious complications, or a bedridden state or hospitalisation) | Wait an additional week | Wait an additional week | Withdraw patient |

| **TABLE 2: STOMATITIS** | | | |
|---|---|---|---|
| | **Week after prior 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 additional week | Re-dose unless patient has experienced a previous Grade 3 or 4 stomatitis, in which case wait an additional week | Decrease dose by 25 %; return to 4-week interval or withdraw patient per medical practitioner's assessment |
| **Grade 2** (painful erythema, oedema, or ulcers, but can eat) | Wait an additional week | Wait an additional week | Decrease dose by 25 %; return to 4-week interval or withdraw patient per medical practitioner's assessment |
| **Grade 3** (painful erythema, oedema, or ulcers, but cannot eat) | Wait an additional week | Wait an additional week | Withdraw patient |
| **Grade 4** (requires parenteral or enteral support) | Wait an additional week | Wait an additional week | Withdraw patient |

| **TABLE 3: HAEMATOLOGICAL TOXICITY (ABSOLUTE NEUTROPHIL COUNT (ANC) OR PLATELETS) – MANAGEMENT OF PATIENTS WITH BREAST OR OVARIAN CANCER** | | | |
|---|---|---|---|
| **GRADE** | **ANC** | **PLATELETS** | **MODIFICATION** |
| 1 | 1 500 to 1 900 | 75 000 to 150 000 | Resume treatment with no dose reduction |
| 2 | 1 000 to < 1 500 | 50 000 to < 75 000 | Wait until ANC ≥ 1 500 and platelets ≥ 75 000; re-dose with no dose reduction |
| 3 | 500 to < 1 000 | 25 000 to < 50 000 | Wait until ANC ≥ 1 500 and platelets ≥ 75 000; re-dose with no dose reduction |
| 4 | < 500 | < 25 000 | Wait until ANC ≥ 1 500 and platelets ≥ 75 000; decrease dose by 25 % or continue full dose with growth factor support |

For multiple myeloma patients treated with 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 ≥ 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 | Do not use this cycle if before Day 4; if after Day | Do not dose; if 2 or more doses are not given in a cycle, reduce |

| | | |
|---|---|---|
| of each cycle: Platelet count < 25 000/$mm^3$ Haemoglobin < 8 g/dl ANC < 500/$mm^3$ | 4, reduce next dose by 25 % in the following cycles if bortezomib is reduced for haematologic toxicity* | 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 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 alanine aminotransferase (ALT)/ aspartate aminotransferase (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 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 must not be given by the intramuscular or subcutaneous route.

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.

**Do not use with in-line filters.**

### 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.
- 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

*Cardiac risk:*

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

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/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 is lower than a prognostically relevant value (e.g., < 45 %), 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 (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 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. 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.

Caution should be taken in patients who have received other anthracyclines.
The total cumulative 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/$m^2$ in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide trastuzumab or other antineoplastic therapy. CHF has been reported, even with doses of 240 to 300 mg/$m^2$ therapy.

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

*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/m$^2$, myelosuppression was generally mild to moderate, reversible, and was not associated with 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 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.

*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/m$^2$. 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 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).

*Palmar-plantar erythrodysaesthesia (PPE):*

The symptoms of PPE include painful, macular reddening skin eruptions. It is generally seen after 2 to 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 to 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 SOPILCIN, 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 SOPILCIN.

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

SOPILCIN 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 SOPILCIN and may be related to opportunistic infections (see section 4.8).

*Extravasation*

Although local necrosis following extravasation has been reported very rarely, SOPILCIN 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. SOPILCIN must not be given by the intramuscular or subcutaneous route.

*Interstitial lung disease (ILD)*

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

*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.

Blood glucose monitoring and adjustment to the antidiabetic treatment may be required.

*Excipients*

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

### 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 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 / Contraception in males and females:*

Due to the genotoxic potential of doxorubicin hydrochloride, women of child bearing potential must be advised to avoid pregnancy and must use highly effective contraception while being treated SOPILCIN and in the 8 months following discontinuation of SOPILCIN therapy.
Men are recommended to use effective contraceptive measures and to not father a child while receiving SOPILCIN and for 6 months following completion of treatment.

*Breastfeeding*

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.

Animal studies showed mild to moderate ovarian and testicular atrophy, decreased testicular weights and hypospermia and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis.

### 4.7 Effects on ability to drive and use machines

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

**a) Summary of the safety profile**

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 liposomal doxorubicin in patients for the treatment of breast cancer, ovarian cancer, multiple myeloma, and AIDS-related KS. Post-marketing adverse reactions are also included.

**TABLE 5: ADVERSE REACTIONS IN PATIENTS TREATED WITH PEGYLATED LIPOSOMAL DOXORUBICIN**

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Infections and infestations | Frequent | Sepsis, pneumonia, *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] |
| 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 disorders | Frequent | Decreased appetite, cachexia, 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 |
| | Less frequent | Palpitations, cardiac arrest, cardiac failure, cardiac failure congestive, cardiomyopathy, cardiotoxicity, dysrhythmia, including |

| | | |
|---|---|---|
| | | ventricular dysrhythmia,<br>bundle branch block right, conduction disorder,<br>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 |
| | Frequency unknown | Interstitial lung disease |
| Gastrointestinal disorders | Frequent | Stomatitis (including aphthous), nausea, vomiting, diarrhoea, constipation, gastritis, , mouth ulceration,<br>dyspepsia, dysphagia, oesophagitis, abdominal pain,<br>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 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 |
| | 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 | 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 |
| | 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<br>[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$^2$ to 1,680 mg/m$^2$. The range of Billingham cardiotoxicity scores was grades 0 to 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 50 mg/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 associate 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 SOPILCIN, 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 SOPILCIN.

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

### 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, a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius var. caesius.*

Doxorubicin is an anthracycline cytostatic antibiotic with activity against a variety of malignancies, including KS. SOPILCIN 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 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 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/m$^2$ to 20 mg/m$^2$) doxorubicin displayed linear pharmacokinetics. Over the dose range of 10 mg/m$^2$ to 60 mg/m$^2$ doxorubicin displayed non-linear pharmacokinetics. Standard doxorubicin hydrochloride displays extensive tissue distribution (volume of

distribution: 700 to 1,100 l/m$^2$) and a rapid elimination clearance (24 to 73 l/h/m$^2$). 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.

*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/m$^2$ (range 0,008 to 0,027 l/h/m$^2$), the mean central volume of distribution was 1,46 l/m$^2$ (range 1,10 to 1,64 l/m$^2$). The mean apparent half-life was 71,5 hours (range 45,2 to 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/m$^2$ in patients with ovarian carcinoma, the mean intrinsic clearance was 0,021 l/h/m$^2$ (range 0,009 to 0,041 l/h/m$^2$), the mean central volume of distribution was 1,95 l/m$^2$ (range 1,67 to 2,40 l/m$^2$). 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/m$^2$. 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 KS patients:*

The plasma pharmacokinetics of doxorubicin were evaluated in 23 patients with KS who received single doses of 20 mg/m$^2$ 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/m$^2$ doses are presented in **TABLE 6**.

| **TABLE 6 Pharmacokinetic parameters in 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 (mcg/ml.h) | 590 ± 58,7 |
| $\lambda_1$ half-life (hours) | 5,2 ± 1,4 |
| $\lambda_2$ 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).

*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 ≥ 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 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

*Unopened vial:*

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 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 to 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).
- Draw up the appropriate volume of SOPILCIN up into a 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

## 10 DATE OF REVISION OF THE TEXT

20 May 2026