PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LEVUSPOZ 50 (powder for solution for infusion)

LEVUSPOZ 100 (powder for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LEVUSPOZ 50: Each vial contains 50,86 mg micafungin sodium equivalent to 50 mg of micafungin.

Contains sugar: Lactose monohydrate 223,15 mg per vial

LEVUSPOZ 100: Each vial contains 101,73 mg micafungin sodium equivalent to 100 mg of micafungin.

Contains sugar: Lactose monohydrate 223,15 mg per vial

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Micafungin powder for solution for infusion.

LEVUSPOZ 50: Solid white to off white cake.

LEVUSPOZ 100: Solid white to off white cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LEVUSPOZ is indicated for:

- Adults, adolescents ≥16 years of age and elderly:
  - Treatment of invasive *candidiasis*.
  - Treatment of oesophageal *candidiasis* in patients for whom intravenous therapy is appropriate.
  - Prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/µl) for 10 or more days.
- Children (including neonates) and adolescents <16 years of age:
  - Treatment of invasive *candidiasis*.
  - Prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/µl) for 10 or more days.

Commonly susceptible species [MIC ranges in Europe, mg/L] *in vitro*

Candida albicans [0,007 – 0,25], *Candida glabrata* [0,007 – 0,12], *Candida tropicalis* [0,007 – 0,12], *Candida krusei* [0,015 – 0,12], *Candida kefyr* [0,03 – 0,06], *Candida parapsilosis* [0,12 – 2], *Candida guilliermondii* [0,5], *Candida lusitaniae* [0,12 – 0,25], *Candida spp.* [0,015 – 0,5], (incl. *C. famata, C. dubliniensis, C. lipolytica, C. pelliculosa, C. rugosa, C. stellatoidea and C. zeylanoides*), *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus terreus, Aspergillus nidulans, Aspergillus versicolor*

The mycelial form of dimorphic fungi (e.g. *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis*).

The decision to use LEVUSPOZ should take into account a potential risk for the development of liver tumours. LEVUSPOZ should therefore only be used if other antifungals are not appropriate (See Section 4.4).

4.2 Posology and Method of Administration

Treatment with LEVUSPOZ should be initiated by a medical practitioner experienced in the management of fungal infections.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Posology

The dose regimen of LEVUSPOZ depends on the body weight of the patient as given in the following tables:

Table 1: Use in adults, adolescents ≥ 16 years of age and elderly

Indication		
	Body weight >40 kg	Body weight ≤ 40 kg
Treatment of invasive *candidiasis*	100 mg/day*	2 mg/kg/day
Treatment of oesophageal *candidiasis*	150 mg/day	3 mg/kg/day
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

*If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients ≤ 40 kg.

Special populations

Use in patients with hepatic impairment:

No dose adjustment is necessary in patients with mild or moderate hepatic impairment. There are currently insufficient data available for the use of micafungin in patients with severe hepatic impairment and its use is not recommended in these patients (See Section 4.4 and 4.8).

Use in patients with renal impairment:

No dose adjustment is necessary in patients with renal impairment.

Paediatric population

Table 2: Use in children ≥ 4 months of age up to adolescents < 16 years of age

Indication		
	Body weight >40 kg	Body weight ≤ 40 kg
Treatment of invasive *candidiasis*	100 mg/day*	2 mg/kg/day
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

*If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg.

Table 3: Use in children (including neonates) < 4 months

Indication	
Treatment of invasive *candidiasis*	4 -10 mg/kg/day*

Prophylaxis of *Candida* infection	2 mg/kg/day

*Micafungin as contained in LEVUSPOZ, dosed at 4 mg/kg in children less than 4 months approximates medicine exposures achieved in adults receiving 100 mg/day for the treatment of invasive *candidiasis*. If central nervous system (CNS) infection is suspected, a higher dosage (e.g. 10 mg/kg) should be used due to the dose-dependent penetration of micafungin into the CNS. The safety and efficacy in children (including neonates) less than 4 months of age of doses of 4 and 10 mg/kg for the treatment of invasive *candidiasis* with CNS involvement has not been adequately reported in controlled clinical studies.

Treatment duration

Invasive *candidiasis*: The treatment duration of *Candida* infection should be a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and ***after*** resolution of clinical signs and symptoms of infection.

Oesophageal *candidiasis*: For the treatment of oesophageal *candidiasis*, LEVUSPOZ should be administered for at least one week after resolution of clinical signs and symptoms.

Prophylaxis of *Candida* infections: For prophylaxis of *Candida* infection, LEVUSPOZ should be administered for at least one week after neutrophil recovery. Experience with micafungin in patients less than 2 years of age is limited.

4.3 Contraindications

- Hypersensitivity to the active substance micafungin, to other echinocandins or to any of the excipients of LEVUSPOZ (see section 6.1).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Hepatic effects:

The development of foci of altered hepatocytes (FAH) and hepatocellular tumours after a treatment period of 3 months or longer were reported in rats. The assumed threshold for tumour development in rats is approximately in the range of clinical exposure. The relevance of this finding for the therapeutic use in patients cannot be excluded. Liver function should be carefully monitored during LEVUSPOZ treatment. To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended. LEVUSPOZ treatment should be conducted on a careful risk/benefit basis, particularly in patients having severe liver function impairment or chronic liver diseases known to represent preneoplastic conditions, such as advanced liver fibrosis, cirrhosis, viral hepatitis, neonatal liver disease or congenital enzyme defects, or receiving a concomitant therapy including hepatotoxic and/or genotoxic properties.

Micafungin (as contained in LEVUSPOZ) treatment is reported to be associated with

significant impairment of liver function (increase of ALT, AST or total bilirubin >3 times ULN) in both healthy volunteers and patients. In some patients more severe hepatic dysfunction, hepatitis, or hepatic failure including fatal cases have been reported. Paediatric patients <1 year of age might be more prone to liver injury.

Anaphylactic reactions:

During administration of LEVUSPOZ, anaphylactic/anaphylactoid reactions including shock may occur. If these reactions occur, LEVUSPOZ infusion should be discontinued and appropriate treatment administered.

Symptoms such as rash and rigors have been reported in clinical studies. The majority were of mild to moderate intensity and not treatment limiting. Serious reactions (e.g. anaphylactoid reaction 0,2 %) were commonly reported during therapy with micafungin as contained in LEVUSPOZ and only in patients with serious underlying conditions (e.g. advanced AIDS, malignancies) requiring multiple co-medications.

Skin reactions:

Exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. If patients develop a rash they should be monitored closely and LEVUSPOZ discontinued if lesions progress.

Haemolysis:

Cases of haemolysis including acute intravascular haemolysis or haemolytic anaemia have been reported in patients treated with micafungin as contained in LEVUSPOZ. Patients who develop clinical or laboratory evidence of haemolysis during LEVUSPOZ therapy should be monitored closely for evidence of worsening of these conditions and

evaluated for the risk/benefit of continuing LEVUSPOZ therapy.

Renal effects:

LEVUSPOZ may cause kidney problems, renal failure, and abnormal renal function tests. Patients should be closely monitored for worsening of renal function.

Interactions with other medicines:

A total of 14 clinical interaction studies conducted in healthy volunteers to evaluate the potential for interaction between micafungin and mycophenolate mofetil, ciclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, rifampicin, amphotericin B, itraconazole and voriconazole were reported. In these reported studies, no interaction that altered the pharmacokinetics of micafungin as contained in LEVUSPOZ was reported. Exposure (AUC) of sirolimus was reported to be increased in the presence of micafungin (21 %). Patients receiving sirolimus in combination with LEVUSPOZ should be monitored for sirolimus toxicity and the sirolimus dosage should be adjusted if necessary.

Human reproduction:

LEVUSPOZ must not be used during pregnancy and lactation. Mothers receiving LEVUSPOZ must not breastfeed their infants (see section 4.3 and 4.6).

Excipients

Lactose Monohydrate

LEVUSPOZ 50 and 100 contains 223,15 mg lactose monohydrate per vial. Patients with rare hereditary problems of galactose intolerance total lactase deficiency or glucose-

galactose malabsorption should not take LEVUSPOZ. This should be taken into account in patients with diabetes mellitus.

Paediatric population:

The incidence of some adverse reactions was reported to be higher in paediatric patients than in adult patients (See section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Micafungin has a low potential for interactions with medicines metabolised via CYP3A mediated pathways.

Reported interaction studies in healthy human subjects were conducted to evaluate the potential for interaction between micafungin and mycophenolate mofetil, ciclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, rifampicin, itraconazole, voriconazole and amphotericin B. In these reported studies, no evidence of altered pharmacokinetics of micafungin was observed. No LEVUSPOZ dose adjustments are necessary when these medicines are administered concomitantly.

Exposure (AUC) of itraconazole, sirolimus and nifedipine was reported to be slightly increased in the presence of micafungin (22 %, 21 % and 18 % respectively).
Co-administration of micafungin and amphotericin B desoxycholate was associated with a 30 % increase in amphotericin B desoxycholate exposure. Since this may be of clinical significance this co-administration should only be used with close monitoring of amphotericin B desoxycholate toxicities. Patients receiving sirolimus, nifedipine or itraconazole in combination with LEVUSPOZ should be monitored for sirolimus,

nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary (See section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

LEVUSPOZ is contraindicated in pregnancy (see section 4.3).

In reported animal studies, micafungin crossed the placental barrier and reproductive toxicity was reported.

Breast-feeding

LEVUSPOZ is contraindicated in lactation (See section 4.3).

Mothers receiving LEVUSPOZ must not breastfeed their infants.

Fertility

Testicular toxicity was reported in animal studies. LEVUSPOZ may have the potential to affect male fertility in humans.

4.7 Effects on ability to drive and use machines

Adverse reactions such as dizziness may occur, which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

Overall 32,2 % of the patients have been reported to experience adverse drug reactions. The most frequently reported adverse reactions were nausea, blood alkaline

phosphatase increased (2,7 %), phlebitis (primarily in HIV infected patients with peripheral lines), vomiting and aspartate aminotransferase increased. No clinically significant differences were reported when the safety data were analysed by gender or race.

b) Tabulated summary of adverse reactions

In the following table, adverse reactions are listed by system organ class and MedDRA preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequent	Less frequent	Frequency not known
Blood and lymphatic system disorders	leukopenia, neutropenia, anaemia	pancytopenia, thrombocytopenia, eosinophilia, hypoalbuminaemia, haemolytic anaemia, haemolysis	disseminated intravascular coagulation
Immune system disorders		anaphylactic/anaphylactoid reaction, hypersensitivity	
Endocrine disorders		hyperhidrosis	
Metabolism and nutritional disorders	hypokalaemia, hypomagnesaemia hypocalcaemia	hyponatraemia, hyperkalaemia, hypophosphataemia, anorexia	

Psychiatric disorders		insomnia, anxiety, confusion	
Nervous system disorders	headache	somnolence, tremor, dizziness, dysgeusia	
Cardiac disorders		tachycardia, palpitations, bradycardia	
Vascular disorders	phlebitis	hypotension, hypertension, flushing	shock
Respiratory, thoracic and mediastinal disorders		dyspnoea	
Gastrointestinal disorders	nausea, vomiting, diarrhoea, abdominal pain	dyspepsia, constipation	
Hepatobiliary disorders	increased blood alkaline phosphatase,	hepatic failure, increased gammaglutamyltransferase,	hepatocellular damage including fatal cases

	increased aspartate aminotransferase, increased alanine aminotransferase, increased blood bilirubin (including hyperbilirubinaemia), abnormal liver function test	jaundice, cholestasis, hepatomegaly, hepatitis	
Skin and subcutaneous tissue disorders	rash	urticaria, pruritus, erythema	toxic skin eruption, erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis
Renal and urinary disorders		increased blood creatinine, increased blood urea, aggravated renal failure	renal impairment, acute renal failure

General disorders and administration site conditions	pyrexia, rigors	injection site thrombosis, infusion site inflammation, injection site pain, peripheral oedema	
Investigations		increased blood lactate dehydrogenase	

c) Description of selected adverse reactions

Hepatic adverse reactions

The overall incidence of hepatic adverse reactions in the patients treated with micafungin, in reported clinical studies was 8,6 %. The majority of hepatic adverse reactions were reported as mild and moderate. Most frequent reactions were reported to be increase in AP (2,7 %), AST (2,3 %), ALT (2,0 %), blood bilirubin (1,6 %) and liver function test abnormal (1,5 %). Few patients (1,1 %; 0,4 % serious) discontinued treatment due to a hepatic event. Cases of serious hepatic dysfunction reported less frequently.

Possible allergic-like symptoms

Symptoms such as rash and rigors have been reported in clinical studies. The majority were of mild to moderate intensity and not treatment limiting. Serious reactions (e.g. anaphylactoid reaction 0,2 %) were less frequently reported during therapy with micafungin and only in patients with serious underlying conditions (e.g. advanced AIDS,

malignancies) requiring multiple co-medications.

Injection-site reactions

None of the reported injection-site adverse reactions were treatment limiting.

Paediatric patients

The incidence of some adverse reactions (listed below) was reported to be higher in paediatric patients than in adult patients. Additionally, paediatric patients <1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients. The most likely reason for these differences were different underlying conditions compared with adults or older paediatric patients reported in clinical studies. At the time of entering the study, the proportion of paediatric patients with neutropenia was several-fold higher than in adult patients (40,2 % and 7,3 % of children and adults, respectively), as well as allogeneic HSCT (29,4 % and 13,4 %, respectively) and haematological malignancy (29,1 % and 8,7 %, respectively).

Blood and lymphatic system disorders

Frequent: thrombocytopenia

Cardiac disorders

Frequent: tachycardia

Vascular disorders

Frequent : hypertension, hypotension

Hepatobiliary disorders

Frequent : hyperbilirubinaemia, hepatomegaly

Renal and urinary disorders

Frequent: acute renal failure, blood urea increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. 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

There is no experience reported with overdoses of micafungin. In case of overdose, general supportive measures and symptomatic treatment should be administered. Micafungin is highly protein-bound and not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.2.2 Antimicrobial (chemotherapeutic agents): Fungicides

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use, ATC code: J02AX05

Micafungin non-competitively inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall. 1,3-β-D-glucan is not present in mammalian cells. Micafungin exhibits fungicidal activity against most *Candida* species and prominently inhibits actively growing hyphae of *Aspergillus* species.

PK/PD relationship

An additive or synergistic pharmacodynamic interaction of micafungin and amphotericin B was reported in a mouse model of pulmonary aspergillosis (immunosuppression with hydrocortisone, intranasal infection with *Aspergillus fumigatus*).

Mechanism(s) of resistance

Cases of reduced susceptibility and resistance have been reported and cross-resistance with other echinocandins cannot be excluded. Reduced susceptibility to echinocandins has been associated with mutations in the Fks1 gene coding for a major subunit of glucan synthase.

Inherently resistant organisms

Cryptococcus spp., *Pseudallescheria* spp., *Scedosporium* spp., *Fusarium* spp., *Trichosporon* spp., *Zygomycetes* spp.

5.2 Pharmacokinetic properties

Absorption

Pharmacokinetics is reported to be linear over the daily dose range of 12,5 mg to 200 mg and 3 mg/kg to 8 mg/kg. There is no reported evidence of systemic accumulation with repeated administration and steady-state is generally reached within 4 to 5 days.

Distribution

Following intravenous administration, concentrations of micafungin reported a bi-exponential decline. Micafungin is rapidly distributed into tissues. In systemic circulation, micafungin is highly bound to plasma protein (>99 %), primarily to albumin. Binding to albumin is independent of micafungin concentration (10-100 µg/mL). The volume of distribution at steady state (Vss) was reported as approximately 18-19 litres.

Metabolism

Unchanged micafungin is the principal circulating compound in systemic circulation. Micafungin has been reported to be metabolised to several compounds; of these M-1 (catechol form), M-2 (methoxy form of M-1) and M-5 (hydroxylation at the side chain) of micafungin have been detected in systemic circulation. Exposure to these metabolites is low and metabolites do not contribute to the overall efficacy of micafungin. Even though micafungin is a substrate for CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for micafungin metabolism *in vivo*.

Elimination and excretion

The mean terminal half-life is reported as approximately 10-17 hours and stays consistent across doses up to 8 mg/kg and after single and repeated administration. Total clearance was reported as 0,15-0,3 mL/min/kg in healthy subjects and adult patients and is independent of dose after single and repeated administration. Following a single intravenous dose of ^{14}C-micafungin (25 mg) to healthy volunteers, 11,6 % of the radioactivity was recovered in the urine and 71,0 % in the faeces over 28 days. These

reported data indicate that elimination of micafungin is primarily non-renal. In plasma, metabolites M-1 and M-2 were detected only at trace concentrations and metabolite M-5, the more abundant metabolite, accounted for a total of 6,5 % relative to parent compound.

Special populations

Elderly: When administered as a single 1-hour infusion of 50 mg the pharmacokinetics of micafungin in the elderly (aged 66-78 years) were reported to be similar to those in young (20-24 years) subjects. No dose adjustment is necessary for the elderly.

Patients with hepatic impairment: In a reported study in patients with moderate hepatic impairment (Child-Pugh score 7-9), the pharmacokinetics of micafungin did not significantly differ from those in healthy subjects. Therefore, no dose adjustment is necessary for patients with mild to moderate hepatic impairment. In a study performed in patients with severe hepatic impairment (Child-Pugh score 10-12), lower plasma concentrations of micafungin and higher plasma concentrations of the hydroxide metabolite (M-5) were seen compared to healthy subjects. These reported data are insufficient to support a dosing recommendation in patients with severe hepatic impairment.

Patients with renal impairment: Severe renal impairment (Glomerular Filtration Rate [GFR] < 30 mL/min) did not significantly affect the pharmacokinetics of micafungin. No dose adjustment is necessary for patients with renal impairment.

Paediatric patients:

In paediatric patients, micafungin exposure is reported to be dose proportional in the dose range of 0,5-4 mg/kg, and up to 10 mg/kg in infants less than 4 months of age. Clearance is influenced by weight with mean values of weight-adjusted clearance 1,35 times higher in the younger children (4 months to 5 years) and 1,14 times higher in children aged 6 to 11 years. Older children (12-16 years) had reported mean clearance values similar to those determined in adult patients. Mean weight-adjusted clearance in infants less than 4 months of age is reported as approximately 2,6-fold greater than older children (12-16 years) and 2,3-fold greater than in adults. Weight-adjusted clearance differences support weight-based dosing up to body weights within the range of 40 (treatment) to 50 kg (prophylaxis), above which adult dosing is recommended.

Micafungin dosed at 4 mg/kg in infants less than 4 months approximates drug exposures achieved in adults receiving 100 mg/day for the treatment of invasive *candidiasis*. Higher doses (e.g., 10 mg/kg) may be required to treat CNS infection in infants less than 4 months of age as demonstrated by a PK-PD bridging study that showed dose-dependent penetration of micafungin into the CNS to achieve maximum eradication of fungal burden in the CNS tissues. Population PK modeling demonstrated that a dose of 10 mg/kg in infants less than 4 months of age would be sufficient to achieve the target exposure for the treatment of CNS *Candida* infections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose monohydrate (low endotoxin),
- Citric Acid

- Sodium Hydroxide (as solution 0,1 %)
- Water for Injection
- Nitrogen

6.2 Incompatibilities

This medicinal product must not be mixed or co-infused with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

30 Months

6.4 Special precautions for storage

Store at or below 30 ºC. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

Reconstituted concentrate in vial:

Chemical and physical in-use stability has been demonstrated for up to 48 hours at 25 °C when reconstituted with sodium chloride 9 mg/mL (0,9 %) solution for infusion or glucose 50 mg/mL (5 %) solution for infusion.

Diluted infusion solution:

Chemical and physical in-use stability has been demonstrated for 96 hours at 25 °C when protected from light when diluted with sodium chloride 9 mg/mL (0,9 %) solution for infusion or glucose 50 mg/mL (5 %) solution for infusion.

LEVUSPOZ contains no preservatives. From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would normally not be longer than 24 hours at 2 to 8 °C, unless the reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

One or five clear, amber glass vials with a rubber stopper and aluminium closure with red or blue plasctic disc, containing solid white to off white powder, packed in a carton box together with the leaflet.

6.6 Special precautions for disposal

Instructions for reconstitution and dilution:

After reconstitution and dilution, the solution should be administered by intravenous infusion over approximately 1 hour. More rapid infusions may result in more frequent histamine mediated reactions.

LEVUSPOZ must not be mixed or co-infused with other medicinal products except those mentioned below. Using aseptic techniques at room temperature, LEVUSPOZ is reconstituted and diluted as follows:

1. The plastic cap must be removed from the vial and the stopper disinfected with alcohol.

2. 5 mL of sodium chloride 9 mg/mL (0,9 %) solution for infusion or glucose 50 mg/mL (5 %) solution for infusion (taken from a 100 mL bottle/bag) should be aseptically and slowly injected into each vial along the side of the inner wall. Although the concentrate will foam, every effort should be made to minimise the amount of foam generated. A sufficient number of vials of LEVUSPOZ must be reconstituted to obtain the required dose in mg (see table below).

3. The vial should be rotated gently. DO NOT SHAKE. The powder will dissolve completely. The concentrate should be used immediately. The vial is for single use only. Therefore, please discard unused reconstituted concentrate immediately.

4. All of the reconstituted concentrate should be withdrawn from each vial and returned into the infusion bottle/bag from which it was originally taken. The diluted infusion solution should be used immediately. Chemical and physical in-use stability has been demonstrated for 96 hours at 25 °C when protected from light and diluted as described above.

5. The infusion bottle/bag should be gently inverted to disperse the diluted solution but NOT agitated in order to avoid foaming. Do not use if the solution is cloudy or has precipitated.

6.The infusion bottle/bag containing the diluted infusion solution should be inserted into a closable opaque bag for protection from light.

Table 3: Preparation of the solution for infusion:

Dose (mg)	LEVUSPOZ vial to be used (mg/vial)	Volume of sodium chloride (0,9 %) or glucose (5 %) to be added per vial	Volume (concentration) of reconstituted powder	Standard infusion (added up to 100 mL) Final concentration
50	1x 50	5 mL	Approx. 5 mL (10 mg/mL)	0,5 mg/mL
100	1x 100	5 mL	Approx. 5 mL (20 mg/mL)	1,0 mg/mL
150	1 x 100 + 1 x 50	5 mL	Approx. 10 mL	1,5 mg/mL
200	2 x 100	5 mL	Approx. 10 mL	2,0 mg/mL

After reconstitution and dilution, the solution should be administered by intravenous infusion over approximately 1 hour.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICAL (PTY) LTD

14 Lautre Road, Stormill, Ext.1

Roodepoort, Johannesburg,

1724

8. REGISTRATION NUMBER(S)

LEVUSPOZ 50 : 57/20.2.2/0119

LEVUSPOZ 100: 57/20.2.2/0120

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 July 2023

10. DATE OF REVISION OF THE TEXT

25 July 2023