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 10 mL 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 10 Ml 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, increased aspartate aminotransferase, increased alanine	hepatic failure, increased gammaglutamyltransferase, jaundice, cholestasis, hepatomegaly,	hepatocellular damage including fatal cases

	aminotransferase, increased blood bilirubin (including hyperbilirubinaemia), abnormal liver function test	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

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

Namibia:
LEVUSPOZ 50: NS2 23/20.1.7/0061

LEVUSPOZ 100: NS2 23/20.1.7/0062

Botswana:
LEVUSPOZ 50: S2 BOT2304079

LEVUSPOZ 100: S2 BOT2304080

PROFESSIONELE INLIGTING

SKEDULINGSTATUS

S4

1. NAAM VAN DIE MEDISYNE

LEVUSPOZ 50 (poeier vir oplossing vir infusie)

LEVUSPOZ 100 (poeier vir oplossing vir infusie)

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

LEVUSPOZ 50: Elke flessie bevat 50,86 mg natriummikafungin gelykstaande aan 50 mg mikafungin.

Bevat suiker: Laktosemonohidraat 223,15 mg per flessie

LEVUSPOZ 100: Elke flessie bevat 101,73 mg natriummikafungin gelykstaande aan 100 mg mikafungin.

Bevat suiker: Laktosemonohidraat 223,15 mg per flessie

Vir volledige lys van onaktiewe bestanddele, sien afdeling 6.1.

3. FARMASEUTIESE VORM

Mikafungin poeier vir oplossing vir infusie.

LEVUSPOZ 50: Soliede wit tot naaswit koekie.

LEVUSPOZ 100: Soliede wit tot naaswit koekie.

4. KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

LEVUSPOZ word aangedui vir:

- Volwassenes, adolessente ≥16-jarige ouderdom en bejaardes:
  - Behandeling van indringende kandidiase.
  - Behandeling van esofageale kandidiase by pasiënte vir wie intraveneuse terapie toepaslik is.
  - Profilakse van *Candida*-infeksie in pasiënte wat allogeneïese hematopoïetiese stamseloorplanting ondergaan of pasiënte wat vermoed word om neutropenie te hê (absolute neutrofieltelling <500 selle/µl) vir 10 of meer dae.
- Kinders (insluitend suigelinge) en adolessente <16-jarige ouderdom:
  - Behandeling van indringende kandidiase.
  - Profilakse van *Candida*-infeksie in pasiënte wat allogeneïese hematopoïetiese stamseloorplanting ondergaan of pasiënte wat vermoed word om neutropenie te hê (absolute neutrofieltelling <500 selle/µl) vir 10 of meer dae.

Algemene vatbare spesies [MIK-reekse in Europa, 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], (insluitend *C. famata, C. dubliniensis, C. lipolytica, C. pelliculosa, C. rugosa, C. stellatoidea en C. zeylanoides*), *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus terreus, Aspergillus nidulans, Aspergillus versicolor*

Die miseliële vorm van dimorfiese fungi (bv. *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis*).

Die besluit om LEVUSPOZ te gebruik, moet die moontlike risiko vir die ontwikkeling van lewertumore in ag neem. LEVUSPOZ moet daarom slegs gebruik word as ander antifungusmiddels nie toepaslik is nie (sien afdeling 4.4).

4.2 Posologie en Metode van Toediening

Behandeling met LEVUSPOZ moet deur 'n dokter wat ervaring het in die beheer van fungusinfeksies geïnisieer word.

Monsters van funguskulture en ander relevante laboratoriumstudies (insluitend histopatologie) moet verkry voor terapie word om oorsaaklike organisme(s) te isoleer en te identifiseer. Terapie kan toegepas word voordat die resultate van die kwekeings en ander laboratoriumstudies bekend is. Wanneer hierdie resultate beskikbaar is, moet antifungusterapie egter daarvolgens aangepas word.

Posologie

Die dosisregimen van LEVUSPOZ hang af van die liggaamsgewig van die pasiënt soos in die volgende tabelle aangedui word:

Tabel 1: Gebruik in volwassenes, adolessente ≥ 16-jarige ouderdom en bejaardes

Indikasie		
	Liggaamsgewig > 40 kg	Liggaamsgewig ≤ 40 kg
Behandeling van indringende kandidiase	100 mg/dag*	2 mg/kg/dag
Behandeling van esofageale kandidiase	150 mg/dag	3 mg/kg/dag
Profilsakse van *Candida*-infeksie	50 mg/dag	1 mg/kg/dag

*As die pasiënt se respons onvoldoende is, bv. volharding van kwekeings of as kliniese toestand nie verbeter nie, kan die dosis tot 200 mg/dag verhoog word in pasiënte wat

> 40 kg weeg of 4 mg/kg/dag in pasiënte ≤ 40 kg.

Spesiale populasies

Gebruik in pasiënte met lewerinkorting:

Geen dosisaanpassing is nodig in pasiënte met ligte tot matige lewerinkorting nie. Daar is huidiglik onvoldoende data beskikbaar vir die gebruik van mikafungin in pasiënte met ernstige lewerinkorting en die gebruik word nie by hierdie pasiënte aanbeveel nie (sien afdeling 4.4 en 4.8).

Gebruik in pasiënte met nierinkorting:

Geen dosisaanpassing is nodig in pasiënte met nierinkorting nie.

Pediatriese populasie

Tabel 2: Gebruik in kinders van ouderdom ≥ 4 maande tot by adolessente < 16-jarige ouderdom

Indikasie		
	Liggaamsgewig > 40 kg	Liggaamsgewig ≤ 40 kg
Behandeling van indringende kandidiase	100 mg/dag*	2 mg/kg/dag
Profilakse van *Candida*-infeksie	50 mg/dag	1 mg/kg/dag

*As die pasiënt se respons onvoldoende is, bv. volharding van kwekings of as kliniese toestand nie verbeter nie, kan die dosis tot 200 mg/dag in pasiënte wat > 40 kg weeg of 4 mg/kg/dag in pasiënte ≤ 40 kg.

Tabel 3: Gebruik in kinders (insluitend pasgeborenes) < 4 maande

Indikasie	
Behandeling van indringende kandidiase	4 -10 mg/kg/dag*

Profilakse van *Candida*-infeksie	2 mg/kg/dag

*Mikafungin soos bevat in LEVUSPOZ, gedoseer teen 4 mg/kg in kinders jonger as 4 maande word by benadering dieselfde mediese blootstellings bereik as in volwassenes wat 100 mg/dag vir die behandeling van indringende kandidiase ontvang het. As sentrale senuweestelsel (SSS)-infeksie vermoed word, moet ‘n hoër dosering (bv. 10 mg/kg) gebruik word as gevolg van die dosis-afhanklike penetrasie van mikafungin binne-in die SSS. Die veiligheid en doeltreffendheid in kinders (insluitend pasgeborenes) jonger as die ouderdom van 4 maande vir dosisse van 4 en 10 mg/kg vir die behandeling van indringende kandidiase met SSS betrokkenheid, is nie voldoende aangemeld in gekontrolleerde kliniese studies nie.

Duur van behandeling

Indringende kandidiase: Die duur van behandeling van *Candida*-infeksie moet ‘n minimum van 14 dae wees. Die antifungusbehandeling moet vir ten minste een week n voortduur nadat opeenvolgende negatiewe bloedkwekings verkry is en ***na*** opklaring van kliniese tekens en simptome van infeksie.

Esofageale kandidiase: Vir die behandeling van esofageale kandidiase, moet LEVUSPOZ vir ten minste een week na opklaring van kliniese tekens en simptome toegedien word.

Profilakse van *Candida*-infeksies: Vir profilakse van *Candida*-infeksie, moet LEVUSPOZ vir ten minste een week na neutrofiel-herstel toegedien word. Ondervinding met mikafungin in pasiënte jonger as 2-jarige ouderdom is beperk.

4.3 Kontra-indiksies

- Hipersensitiwiteit teen die aktiewe bestanddeel, mikafungin, teen ander ekinokandiene of teen enige van die onaktiewe bestanddele van LEVUSPOZ (sien afdeling 6.1).
- Swangerskap en laktasie (sien afdeling 4.6).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Hepatiese effekte:

Die ontwikkeling van foci of veranderde hepatosiete (FAH) en hepatosellulêre tumore na ’n behandelingstydperk van 3 maande of langer is aangemeld in rotte. Die veronderstelde drempel vir tumorontwikkelling in rotte is ongeveer in die reikwydte van kliniese blootstelling. Die toepaslikheid van hierdie bevinding vir die terapeutiese gebruik in pasiënte kan nie uitgesluit word nie. Lewerfunksie moet noukeurig gemonitor word tydens LEVUSPOZ-behandeling. Om die risiko van aangepaste regenerasie en moontlike opeenvolgende lewertumor-vorming te minimaliseer, word vroeë staking in die teenwoordigheid van merkbare en volgehoue verhoging van ALT/AST aanbeveel. LEVUSPOZ-behandeling moet op ‘n versigtige risiko/voordeel-basis uitgevoer word, veral in pasiënte wat ernstige lewerfunksie-ontoereikendheid of chroniese lewersiektes het wat bekend is daarvoor om pre-neoplastiese toestande te verteenwoordig, soos gevorderde lewerfibrose, sirrose, virale hepatitis, neonatale lewersiekte of kongenitale ensiemdefekte, of wat ‘n gelyktydige terapie ontvang insluitend hepatoksiese en/of genotoksiese eienskappe.

Mikafungin (soos bevat in LEVUSPOZ)-behandeling is aangemeld om geassosieer te word met merkbare inkorting van lewerfunksie (verhoging van ALT, AST of totale bilirubien >3 keer ULN) in beide gesonde proefpersone en in pasiënte. In sommige pasiënte is meer ernstige hepatiese wanfunksie, hepatitis, of lewerversaking insluitend noodlottige gevalle, aangemeld. Pediatriese pasiënte <1-jarige ouderdom mag meer geneig wees tot lewerbeskadiging.

Anafilaktiese reaksies:

Tydens toediening van LEVUSPOZ, kan anafilaktiese/anafilaktoïede reaksies, insluitend skok, voorkom. As hierdie reaksies voorkom, moet LEVUSPOZ-infusie gestaak word en toepaslike behandeling toegedien word.

Simptome soos uitslag en koudheid is aangemeld in kliniese studies. Die meerderheid is van ligte tot matige intensiteit en nie beperkend vir behandeling nie. Ernstige reaksies (bv. 0,2 % anafilaktoïede reaksie) word algemeen aangemeld tydens terapie met mikafungin soos bevat in LEVUSPOZ en slegs in pasiënte met ernstige onderliggende toestande (bv. gevorderde VIGS, kwaadaardighede) wat veelvuldige gelyktydige medikasie vereis.

Velreaksies:

Afskilferende kutaneuse reaksies, soos Stevens-Johnson se sindroom en toksiese epidermale nekrolise is aangemeld. As pasiënte ‘n uitslag ontwikkel, moet hul noukeurig gemonitor word en LEVUSPOZ moet gestaak word as letsels voortduur.

Hemolise:

Gevalle van hemolise insluitend akute intravaskulêre hemolise of hemolitiese anemie is

aangemeld in pasiënte wat met mikafungin, soos bevat in LEVUSPOZ, behandel is. Pasiënte wat kliniese of laboratoriumbewyse van hemolise ontwikkel tydens LEVUSPOZ-terapie moet noukeurig gemonitor word vir bewyse van verergering van hierdie toestande en geëvalueer word vir die risiko/voordeel met voortduur van LEVUSPOZ-terapie.

Renale effekte:

LEVUSPOZ kan nierprobleme, nierversaking, en abnormale nierfunksietoetse veroorsaak. Pasiënte moet noukeurig gemonitor word vir verergering van nierfunksie.

Interaksies met ander medisyne:

‘n Totaal van 14 kliniese interaksie-studies uitgevoer in gesonde vrywilligers om die moontlike interaksie tussen mikafungin en mikofenilaatmofetiel, siklosporien, takrolimus, prednisoloon, sirolimus, nifedipien, flukonasool, ritonavir, rifampisien, amfoterisien-B, itrakonasool en vorikonasool te evalueer, is aangemeld. In hierdie aangemelde studies, is geen interaksie wat die farmakokinetika van mikafungin, soos bevat LEVUSPOZ, verander, aangemeld nie. Blootstelling (AOK) van sirolimus is aangemeld om te verhoog in die teenwoordigheid van mikafungin (21 %). Pasiënte wat sirolimus ontvang in kombinasie met LEVUSPOZ, moet vir sirolimustoksisiteit gemonitor word en die sirolimusdosis moet aangepas word indien nodig.

Menslike voortplanting:

LEVUSPOZ moet nie tydens swangerskap of laktasie gebruik word nie. Moeders wat LEVUSPOZ ontvang, moet nie hulle suigelinge borsvoed nie (sien afdeling 4.3 en 4.6).

Onaktiewe bestanddele

Laktosemonohidraat

LEVUSPOZ 50 en 100 bevat 223,15 mg laktosemonohidraat per flessie. Pasiënte met die seldsame oorerflike probleme van galaktose onverdraagsaamheid, totale laktase tekort of glukose-galaktose wanabsorpsie moet nie LEVUSPOZ ontvang nie. Dit moet in gedagte gehou word in pasiënte met diabetes mellitus.

Pediatriese populasie:

Die voorkoms van sommige ongewenste reaksies is aangemeld om hoër te wees in pediatriese pasiënte as in volwasse pasiënte (sien afdeling 4.8).

4.5 Interaksie met ander medisyne en ander vorme van interaksie

Mikafungin besit ‘n lae potensiaal vir interaksies met medisyne wat *via* CYP3A-bemiddelde bane gemetaboliseer word.

Aangemelde interaksie-studies in gesonde menslike proefpersone is uitgevoer om die moontlikheid van interaksie tussen mikafungin en mikofenilaatmofetiel, siklosporien, takrolimus, prednisoloon, sirolimus, nifedipien, flukonasool, ritonavir, rifampisien, itrakonasool, vorikonasool en amfoterisien-B te evalueer. In hierdie aangemelde studies is geen bewys van veranderde farmakokinetika van mikafungin waargeneem nie. Geen LEVUSPOZ-dosisaanpassings is nodig wanneer hierdie medisyne gelyktydig toegedien word nie.

Blootstelling (AOK) van itrakonasool, sirolimus en nifedipien is aangemeld om effens verhoog te wees in die teenwoordigheid van mikafungin (22 %, 21 % en 18 %,

respektiewelik).

Gelyktydige toediening van mikafungin en amfoterisien-B-desoksiecholaat is geassosieer met ‘n 30 % toename in amfoterisien-B-desoksicholaat-blootstelling. Aangesien dit van kliniese belang kan wees, moet hierdie gelyktydige toediening slegs gebruik word met noukeurige monitering van amfoterisien-B-desoksiecholaat-toksisiteite. Pasiënte wat sirolimus, nifedipien of itrakonasool in kombinasie met LEVUSPOZ ontvang, moet gemonitor word vir sirolimus, nifedipien of itrakonasool-toksisiteit en die sirolimus, nifedipien of itrakonasool-dosering moet verlaag word indien nodig (sien afdeling 4.4).

4.6 Fertiliteit, swangerskap en laktasie

Swangerskap

LEVUSPOZ is teenaangedui in swangerskap (sien afdeling 4.3).

In aangemelde dierestudies, kruis mikafungin die plasentale skans en voortplantingstoksisiteit is aangemeld.

Borsvoeding

LEVUSPOZ is teenaangedui in laktasie (sien afdeling 4.3).

Moeders wat LEVUSPOZ ontvang, moet nie hulle suigelinge borsvoed nie.

Fertiliteit

Testikulêre toksisiteit is aangemeld in dierestudies. LEVUSPOZ kan die potensiaal hê om manlike fertiliteit in mense te affekteer.

4.7 Effekte op die vermoë om te bestuur en masjinerie te gebruik

Ongunstige reaksies, soos duiseligheid, kan voorkom, wat 'n invloed kan hê op die vermoë om te bestuur of masjinerie te gebruik (sien afdeling 4.8).

4.8 Ongewenste effekte

a) Opsomming van die veiligheidsprofiel

Ongunstige geneesmiddelreaksies is aangemeld om by oor die algeheel 32,2 % van die pasiënte ervaar te word. Die mees algemene aangemelde ongunstige reaksies was naarheid, bloed-alkaliese fosfatase verhoging (2,7 %), flebitis (primêr in MIV-geïnfekteerde pasiënte met periferale lyne), braking en aspartaat-aminotransferase verhoging. Geen klinies-betekenisvolle verskille is aangemeld wanneer die veiligheidsdata deur geslag of ras ge-analiseer is nie.

b) Getabuleerde opsomming van ongunstige reaksies

In die volgende tabel word ongunstige reaksies volgens orgaanklas en MedDRA voorkeurterm gelys. Binne elke voorkomsgroep, word ongunstige reaksies aangedui in volgorde van dalende ernstigheid.

Sisteem Orgaanklas	**Dikwels**	**Minder dikwels**	**Voorkoms onbekend**
Bloed- en limfatiese stelsel-versteurings	leukopenie, neutropenie, anemie	pansitopenie, trombositopenie, eosinofilie, hipoalbuminemie, hemolitiese anemie, hemolise	verspreide intravaskulêre koagulasie

Immuun-stelsel-versteurings		anafilaktiese/ anafilaktoïede reaksie, hipersensitiwiteit	
Endokriene versteurings		hiperhidrose	
Metabolisme en voedings-versteurings	hipokalemie, hipomagnesemie hipokalsemie	hiponatremie, hiperkalemie, hipofosfatemie, anoreksie	
Psigiatriese versteurings		slapeloosheid, angstigheid, verwarring	
Senuwee-stelsel-versteurings	hoofpyn	lomerigheid, bewerigheid, duiseligheid, disgeusie	
Kardiale versteurings		tagikardie, palpitasies, bradikardie	
Vaskulêre versteurings	flebitis	hipotensie, hipertensie, blosing	skok
Respiratoriese, torakale en		dispnee	

mediastinale versteurings			
Gastroïntes-tinale versteurings	naarheid, braking, diaree, abdominale pyn	dispepsie, hardlywigheid	
Hepatobiliêre versteurings	verhoogde bloed alkaliese fosfatase, verhoogde aspartaatamino-transferase, verhoogde alanienamino-transferase, verhoogde bloed-bilirubien (insluitend hiperbilirubinemie), abnormale lewerfunksietoets	lewerversaking, verhoogde gammaglutamiel-transferase, geelsug, cholestase, hepatomegalie, hepatitis	hepatosellulêre skade insluitend noodlottige gevalle
Vel- en subkutane weefsel-versteurings	uitslag	urtikarie, pruritus, eriteem	toksiese veluitbarsting, veelvuldige eriteem,

			Stevens-Johnson se sindroom, toksiese epidermale nekrolise
Renale en urinêre versteurings		verhoogde bloed-kreatinien, verhoogde bloedureum, verergerde nierversaking	nierontoereikend-heid, akute nierversaking
Algemene versteurings en toedienplek-toestande	pireksie, rigors	inspuitplektrombose, infuusplek-inflammasie, inspuitplekpyn, periferale edeem	
Ondersoeke		verhoogde bloedlaktaatdehidro-genase	

c) Beskrywing van geselekteerde ongunstige reaksies

Hepatiese ongunstige reaksies

Die algehele voorkoms van hepatiese ongunstige reaksies in aangemelde kliniese studies in die pasiënte wat met mikafungin behandel is, was 8,6 %. Die meerderheid van

hepatiese ongunstige reaksies is aangemeld as lig tot matig. Mees dikwelse reaksies is aangemeld om te verhoog in AP (2,7 %), AST (2,3 %), ALT (2,0 %), bloedbilirubien (1,6 %) en lewerfunksietoets abnormaal (1,5 %). ‘n Paar pasiënte (1,1 %; 0,4 % ernstig) het behandeling gestaak as gevolg van ‘n hepatiese voorval. Gevalle van ernstige hepatiese wanfunksie is minder dikwels aangemeld.

Moontlike allergie-agtige simptome

Simptome soos uitslag en koudheid is aangemeld in kliniese studies. Die meerderheid was van ligte tot matige intensiteit en nie behandelingsbeperkend nie. Ernstige reaksies (bv. 0,2 % anafilaktoïede reaksies) was minder dikwels aangemeld tydens terapie met mikafungin en slegs in pasiënte met ernstige onderliggende toestande (bv. gevorderde VIGS, kwaadaardighede) wat veelvuldige gelyktydige medikasie benodig.

Inspuitplekreaksies

Geen van die aangemelde ongunstige reaksies by die inspuitplek was behandelingsbeperkend nie.

Pediatriese pasiënte

Die voorkoms van sommige ongunstige reaksies (soos hieronder gelys) is aangemeld om hoër te wees as in volwasse pasiënte. Bykomend, pediatriese pasiënte <1-jarige ouderdom ervaar ongeveer twee keer meer dikwels ‘n toename in ALT, AST en AP as ouer pediatriese pasiënte. Die mees waarskynlike rede vir hierdie verskille is verskillende onderliggende toestande vergeleke met volwassenes of ouer pediatriese pasiënte aangemeld in kliniese studies. Teen die tyd van toetrede tot die studie, was die die aantal van pediatriese pasiënte met neutropenie veelvoudig hoër as in volwasse

pasiënte (40,2 % en 7,3 % van kinders en volwassenes, respektiewelik), asook allogeneïese HSCT (29,4 % en 13,4 %, respektiewelik) en hematologiese kwaadaardigheid (29,1 % en 8,7 %, respektiewelik).

Bloed- en limfatiese stelselversteurings

Dikwels: trombositopenie

Kardiale versteurings

Dikwels: tagikardie

Vaskulêre versteurings

Dikwels: hipertensie, hipotensie

Hepatobiliêre versteurings

Dikwels: hiperbilirubinemie, hepatomegalie

Renale en urinêre versteurings

Dikwels: akute nierversaking, verhoogde bloedureum

4.9 Oordosis

Daar is geen ondervinding aangemeld met oordosisse van mikafungin nie. In geval van oordosering, moet algemene ondersteunende maatreëls en simptomatiese behandeling toegepas word. Mikafungin is hoogs-proteïengebonde en nie dialiseerbaar nie.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

A.20.2.2 Antimikrobiese middel (chemoterapeutiese middels): Fungisiede

Farmakoterapeutiese groep: Antimikotika vir sistemiese gebruik, ander antimikotika vir sistemiese gebruik, ATC kode: J02AX05

Mikafungin inhibeer die sintese van 1,3-β-D-glukaan nie-kompetitief, 'n essensiële bestanddeel van die fungusselwand. 1,3-β-D-glukaan is nie in soogdierselle teenwoordig nie.

Mikafungin oefen fungisidiese aktiwiteit uit teen meeste *Candida* spesies en inhibeer voortreflik aktief-groeiende hife van *Aspergillus* spesies.

PK/PD-verwantskap

'n Bykomende of sinergistiese farmakodinamiese interaksie van mikafungin en amfoterisien-B in aangemeld in 'n muis-model van pulmonêre aspergillose (immuunonderdrukking met hidrokortisoon, intranasale infeksie met *Aspergillus fumigatus*).

Meganisme(s) van weerstand

Gevalle van verminderde vatbaarheid en weerstandigheid is aangemeld en kruisweerstandigheid met ander ekinokandiene kan nie uitgesluit word nie. Verminderde vatbaarheid vir ekinokandien is met mutasies in die Fks1 geenkodering vir 'n hoof subeenheid van glukaansintase geassosieer.

Inherente weerstandbiedende organismes

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

5.2 Farmakokinetiese eienskappe

Absorpsie

Farmakokinetika is aangemeld om lineêr te wees oor die daaglikse dosisreeks van 12,5 mg tot 200 mg en 3 mg/kg tot 8 mg/kg. Daar is geen aangemelde bewys van sistemiese akkumulasie met herhaaldelike toediening nie en gelykstaat word gewoonlik binne 4 tot 5 dae bereik.

Verspreiding

Na intraveneuse toediening, toon konsentrasies van mikafungin ‘n twee-voudige afname. Mikafungin word vinnig binne-in weefsels versprei. In sistemiese sirkulasie is mikafungin hoogsgebonde aan plasmaproteïen (> 99 %), hoofsaaklik aan albumien. Binding aan albumien is onafhanklik van mikafungin-konsentrasie (10-100 µg/mL). Die volume van verspreiding by gelykstaat (Vss) is aangemeld as ongeveer 18-19 liter.

Metabolisme

Onveranderde mikafungin is die hoofsirkulerende verbinding in sistemiese sirkulasie. Daar word aangemeld dat mikafungin na verskeie verbindings gemetaboliseer word; van hierdie M-1 (katesjol-vorm), M-2 (metoksi-vorm van M-1) en M-5 (hidroksilering by die syketting) van mikafungin is opgespoor in sistemiese sirkulasie. Blootstelling aan hierdie metaboliete is laag en metaboliete dra nie by tot die oorhoofse doeltreffendheid van mikafungin nie. Selfs al is mikafungin ‘n substraat vir CYP3A *in vitro*, is hidroksilering deur CYP3A nie ‘n hoofbaan vir mikafungin metabolisme *in vivo* nie.

Eliminasie en uitskeiding

Die gemiddelde terminale halfleeftyd word aangemeld as ongeveer 10-17 uur en bly konsekwent oor dosisse tot by 8 mg/kg en na enkel en herhaalde toediening. Totale opruiming is aangemeld as 0,15-0,3 mL/min/kg in gesonde proefpersone en volwasse pasiënte en is onafhanklik van dosis na enkel en herhaaldelike toedoening. Na ‘n enkel intraveneuse dosis van ^{14}C-mikafungin (25 mg) aan gesonde proefpersone, is 11,6 % van die radioaktiwiteit oor 28 dae herwin in die urine en 71,0 % in die feses. Hierdie aangemelde data dui aan dat die eliminasie van mikafungin hoofsaaklik nie-renaal is. In plasma, is metaboliete M-1 en M-2 opgespoor slegs teen spoorkonsentrasies en metaboliet M-5, die meer volop metaboliet, verantwoordelik vir ‘n totaal van 6,5 % relatief tot die moederverbinding.

Spesiale populasies

Bejaardes: Wanneer as ‘n enkel 1-uur infusie van 50 mg toegedien word, is die farmakokinetika van mikafungin in die bejaardes (ouderdom 66-78-jarige) aangemeld as soortgelyk aan dié in jong (20-24-jarige) proefpersone. Geen dosisaanpassing is vir die bejaardes nodig nie.

Pasiënte met hepatiese inkorting: In ‘n aangemelde studie in pasiënte met matige hepatiese inkorting (Child-Pugh telling 7-9), het die farmakokinetika van mikafungin nie merkwaardig verskil van dié in gesonde proefpersone nie. Geen dosisaanpassing is daarom nodig vir pasiënte met ligte tot matige hepatiese inkorting nie. In ‘n studie wat uitgevoer is in pasiënte met ernstige hepatiese inkorting (Child-Pugh telling 10-12), is laer plasmakonsentrasies van mikafungin en hoër plasmakonsentrasies van die

hidroksiedmetaboliet (M-5) waargeneem vergeleke met gesonde proefpersone. Hierdie aangemelde data is voldoende om ‘n dosisaanbeveling in pasiënte met ernstige hepatiese inkorting te ondersteun.

Pasiënte met renale inkorting: Ernstige renale inkorting (Glomerulêre filtrasiespoed [GFR] < 30 mL/min) het nie die farmakokinetika van mikafungin merkwaardig geaffekteer nie. Geen dosisaanpassing is nodig vir pasiënte met renale inkorting nie.

Pediatriese pasiënte:

By pediatriese pasiënte is mikafungin-blootstelling aangemeld om dosis-proporsioneel te wees in die dosisreeks van 0,5-4 mg/kg, en tot by 10 mg/kg in suigelinge van jonger as ‘n ouderdom van 4 maande. Opruiming word beïnvloed deur gewig met gemiddelde waardes van gewigsaangepaste opruiming 1,35 keer hoër in die jonger kinders (4 maande tot 5 jaar) en 1,14 keer hoër in kinders van ouderdom 6 tot 11 jaar. Ouer kinders (12-16 jaar) het gemiddelde opruimingswaardes, soortgelyk aan dié vasgestel in volwasse pasiënte, aangemeld. Gemiddelde gewigsaangepaste opruiming in suigelinge jonger as ‘n ouderdom van 4 maande is aangemeld as ongeveer 2,6-voudig groter as in ouer kinders (12-16-jariges) en 2,3-voudig groter as in volwassenes. Gewigsaangepaste opruimingsverskille ondersteun gewigsgebaseerde dosering tot by liggaamsgewig binne die reeks van 40 (behandeling) tot 50 kg (profilakse), waarbo volwasse dosering aanbeveel word.

Mikfungin gedoseer teen 4 mg/kg in suigelinge onder die ouderdom van 4 maande het benaderde blootstelling aan medisyne in volwassenes wat 100 mg/dag ontvang vir die behandeling van indringende kandidiase. Hoër dosisse (bv. 10 mg/kg) mag nodig wees

om SSS-infeksie in suigelinge onder die ouderdom van 4 maande te behandel soos aangetoon deur ‘n PK-PD oorbruggings-studie wat dosis-afhanklike penetrasie van mikafungin binne-in die SSS aangetoon het om maksimum vernietiging van die funguslading in die SSS-weefsel te bereik. Populasie PK-modelering het aangetoon dat ‘n dosis van 10 mg/kg in suigelinge wat jonger as ‘n ouderdom van 4 maande is, voldoende sal wees om die doelwit-blootstelling vir die behandeling van SSS-*Candida*-infeksies te bereik.

6. FARMASEUTIESE BESONDERHEDE

6.1 Lys van onaktiewe bestanddele

- Laktosemonohidraat (lae endotoksien),
- Sitroensuur
- Natriumhidroksied (as oplossing 0,1 %)
- Water vir Inspuiting
- Stikstof

6.2 Onverenigbaarhede

Hierdie medisinale produk moet nie gemeng of gelyktydig met ander medisinale produkte in ‘n infuus gebruik word nie, behalwe dié wat in afdeling 6.6 genoem word.

6.3 Rakleeftyd

24 Maande

6.4 Spesiale voorsorgmaatreëls vir bewaring

Bewaar by of onder 30 ºC. Beskerm teen lig.

HOU BUITE DIE BEREIK VAN KINDERS.

Hersaamgestelde konsentraat in flessie:

Chemiese en fisiese in-gebruikstabiliteit is vasgestel vir tot 48 uur by 25 °C wanneer hersaamgestel met natriumchloriedoplossing 9 mg/mL (0,9 %) vir infusie of glukose-oplossing 50 mg/mL (5 %) vir infusie.

Verdunde infusie-oplossing:

Chemiese en fisiese in-gebruikstabiliteit is vasgestel vir 96 uur teen 25 °C wanneer beskerm teen lig wanneer verdun met natriumchloriedoplossing 9 mg/mL (0,9 %) vir infusie of glukose-oplossing 50 mg/mL (5 %) vir infusie.

LEVUSPOZ bevat geen preserveermiddels nie. Vanuit ‘n mikrobiologiese oogpunt moet die hersaamgestelde en verdunde oplossings onmiddellik gebruik word. As nie onmiddelllik gebruik word nie, is die in-gebruiks-bewaringstye en voorwaardes voor gebruik die verantwoordelikheid van die gebruiker en sal gewoonlik nie langer as 24 uur teen 2 tot 8 °C wees nie, tensy die hersamestelling en verdunning onder gekontrolleerde en gevalideerde aseptiese toestande plaasgevind het.

6.5 Aard en inhoud van die houer

5 helder, amberglasflessies met ‘n rubberprop en aluminiumseël met ‘n rooi of blou plastiekdoppie, bevattende ‘n soliede wit tot naaswit poeier verpak in ‘n kartondosie saam met die inligtingstuk.

6.6 Spesiale voorsorgmaatreëls vir vernietiging

Instruksies vir hersamestelling en verdunning:

Na hersamestelling en verdunning moet die oplossing deur intraveneuse infusie oor ongeveer 1 uur toegedien word. Vinniger infusies kan lei tot meer dikwelse histamienbemiddelde reaksies.

LEVUSPOZ moet nie gemeng of saam met ander medisinale produkte as infuus toegedien word nie, behalwe dié wat hieronder genoem word. By hersamestelling van LEVUSPOZ, gebruik aseptiese tegnieke by kamertemperatuur en verdun as volg:

1. Die plastiekdoppie moet verwyder word vanaf die flessie en die prop met alkohol gedisinfekteer word.
2. 5 mL natriumchloried 9 mg/mL (0,9 %) oplossing vir infusie of glukose 50 mg/mL (5 %) oplossing vir infusie (geneem van ‘n 100 mL bottel/sakkie) moet asepties en stadig in elke flessie teen die binneste wand ingespuit word. Alhoewel die konsentraat sal skuim, moet elke poging aangewend word om die hoeveelheid skuim wat gevorm word, te minimaliseer. ‘n Voldoende aantal flessies van LEVUSPOZ moet hersaamgestel word om die verlangde dosis in mg te verkry (sien tabel hieronder).
3. Die flessie moet saggies geroteer word. MOENIE SKUD NIE. Die poeier sal volledig oplos. Die konsentraat moet onmiddellik gebruik word. Die flessie is slegs vir enkelgebruik. Vernietig asseblief daarom ongebruikte hersaamgestelde konsentraat onmiddellik.
4. Al die hersaamgestelde konsentraat moet van elke flessie opgetrek word en teruggespuit word binne-in die infuusbottel/sakkie waarvandaan dit oorspronklik geneem is. Die verdunde infusie-oplossing moet onmiddellik gebruik word. Chemiese en fisiese ingebruikstabiliteit is vasgestel vir 96 uur teen 25 °C wanneer beskerm teen lig en verdun soos hierbo beskryf.

5. Die infuusbottel/sakkie moet versigtig omgedraai word om die verdunde oplossing te versprei maar NIE geskud word nie om skuimvorming te verhoed. Moenie die oplossing gebruik as dit troebel is of gepresipiteer het nie.

6. Die infuusbottel/sakkie wat die verdunde infusie-oplossing bevat, moet binne-in 'n ondeursigtige sakkie vir beskerming teen lig en wat toegemaak kan word, geplaas word.

Tabel 3: Voorbereiding van die oplossing vir infusie:

Dosis (mg)	LEVUSPOZ flessie om te gebruik (mg/flessie)	Volume van natriumchloried (0,9 %) of glukose (5 %) om by die flessie te voeg	Volume (konsentrasie) van hersaamgestelde poeier	Standaardinfusie (opgemaak tot by 100 mL) Finale konsentrasie
50	1x 50	5 mL	Ongeveer 5 mL (10 mg/mL)	0,5 mg/mL
100	1x 100	5 mL	Ongeveer 5 mL (20 mg/mL)	1,0 mg/mL
150	1 x 100 + 1 x 50	5 mL	Ongeveer 10 mL	1,5 mg/mL
200	2 x 100	5 mL	Ongeveer 10 mL	2,0 mg/mL

Na hersamestelling en verdunning, moet die oplossing deur intraveneuse infusie oor ongeveer 1 uur toegedien word.

7. HOUER VAN DIE REGISTRASIESERTIFIKAAT

RANBAXY PHARMACEUTICALS (PTY) LTD

'n Sun Pharma maatskappy

Lautreweg 14, Stormill, Uitbreiding 1

Roodepoort, Johannesburg,

1724

8. REGISTRASIENOMMERS

9. DATUM VAN EERSTE GOEDKEURING/HERNUWING VAN DIE GOEDKEURING

10. DATUM VAN HERSIENING VAN DIE TEKS