SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vorizest (Voriconazole 200 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Voriconazole BP 200 mg.

Excipient with known effect: Lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voriconazole is a broad-spectrum triazole antifungal agent indicated in adults and children aged 2 years and above for:

- Treatment of invasive aspergillosis.
- Treatment of candidaemia in non-neutropenic patients.
- Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).
- Treatment of oesophageal candidiasis.
- Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.
- Treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy.
- Prophylaxis of invasive fungal infections in high-risk allogeneic haematopoietic stem cell transplant (HSCT) recipients.

Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections.

4.2 Posology and method of administration

Voriconazole tablets are to be taken at least one hour before, or one hour following, a meal.

Use in adults

Therapy is generally initiated with an intravenous loading dose to achieve adequate plasma concentrations on Day 1. Once the patient is clinically improved and able to tolerate oral medication, the tablet formulation may be used. Standard oral maintenance dose: 200 mg every 12 hours (patients ≥40 kg) or 100 mg every 12 hours (patients <40 kg). For candidaemia and oesophageal candidiasis, the same oral maintenance doses apply.

Dosage adjustment: If response is inadequate, the oral maintenance dose may be increased to 300 mg every 12 hours (150 mg every 12 hours for patients <40 kg). If the higher dose is not tolerated, reduce in steps of 50 mg to a minimum of 200 mg every 12 hours (100 mg every 12 hours for patients <40 kg).

Use in the elderly

No dose adjustment is necessary.

Use in patients with renal impairment

The pharmacokinetics of orally administered voriconazole are not affected by renal impairment; no adjustment is necessary for oral dosing in patients with mild to severe renal impairment.

Use in patients with hepatic impairment

No dose adjustment is necessary in patients with acute hepatic injury with elevated liver function tests, though continued monitoring is recommended. The standard loading dose should be used, but the maintenance dose halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B). Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C) and should only be used if the benefit outweighs the risk, with careful monitoring for toxicity.

Use in paediatrics

For children aged 2 to <12 years and young adolescents (12 to 14 years, <50 kg), dosing is weight-based and should follow specialist paediatric dosing recommendations. Voriconazole is not recommended for children under 2 years of age. All other adolescents (12 to 14 years and ≥50 kg; 15 to 16 years regardless of weight) should be dosed as adults.

Method of administration: Oral use.

4.3 Contraindications

Voriconazole is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients.

Co-administration with the following is contraindicated due to risk of QTc prolongation, decreased voriconazole efficacy, or significantly altered plasma concentrations of either agent:

- Terfenadine, astemizole, cisapride, pimozide, quinidine or ivabradine (CYP3A4 substrates — risk of QTc prolongation and torsade de pointes).
- Sirolimus (significantly increased plasma concentrations).
- Rifabutin, rifampicin, carbamazepine, long-acting barbiturates (e.g. phenobarbital), and St John's Wort (significant decrease in plasma voriconazole concentrations).
- Efavirenz at doses of 400 mg once daily or higher, and high-dose ritonavir (400 mg and above twice daily).
- Ergot alkaloids (ergotamine, dihydroergotamine) — risk of ergotism.
- Naloxegol, tolvaptan (significantly increased plasma concentrations).
- Venetoclax, at initiation and during the dose-titration phase (increased risk of tumour lysis syndrome).
- Lurasidone (significant increase in exposure and risk of serious adverse reactions).

4.4 Special warnings and precautions for use

Hypersensitivity: Caution should be used when prescribing voriconazole to patients with hypersensitivity to other azoles.

Cardiac adverse events: Voriconazole has been associated with QT interval prolongation on the ECG. Rare cases of torsade de pointes have been reported, generally in seriously ill patients with confounding risk factors. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, including congenital or acquired QT prolongation, cardiomyopathy, sinus bradycardia, existing symptomatic arrhythmias, or concomitant QT-prolonging medicinal products. Electrolyte disturbances (hypokalaemia, hypomagnesaemia, hypocalcaemia) should be monitored and corrected before and during therapy.

Hepatic toxicity: Serious hepatic reactions have occurred during treatment, including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities, primarily in patients with serious underlying medical conditions. Liver function (AST, ALT) should be evaluated at

initiation of treatment and at least weekly for the first month, then monthly if stable. Voriconazole should be discontinued if liver function tests become markedly elevated, unless the risk-benefit assessment justifies continued use.

Visual adverse events: Post-marketing reports include prolonged visual adverse events, including optic neuritis and papilledema, primarily in severely ill patients with confounding factors.

Renal adverse events: Acute renal failure has been observed in severely ill patients; renal function (particularly serum creatinine) should be monitored.

Pancreatic function: Patients with risk factors for acute pancreatitis (e.g. recent chemotherapy, HSCT) should be monitored during treatment.

Dermatological adverse events: Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS, have occurred and can be life-threatening or fatal; voriconazole should be discontinued if a severe cutaneous reaction develops. Photosensitivity skin reactions have also been reported; patients should avoid direct sunlight exposure and use protective clothing and high-SPF sunscreen during treatment.

Adrenal events: Reversible cases of adrenal insufficiency have been reported, and Cushing's syndrome (with or without subsequent adrenal insufficiency) has been reported in patients receiving voriconazole concomitantly with corticosteroids; patients on long-term combined therapy should be monitored for adrenal cortex dysfunction.

Long-term treatment: Squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy, particularly in patients with photosensitivity reactions; dermatologic evaluation is recommended, and discontinuation should be considered if premalignant or malignant skin lesions develop. Non-infectious periostitis has been reported in transplant patients during long-term therapy; voriconazole should be discontinued if a patient develops skeletal pain with compatible radiologic findings.

Paediatric use: Safety and effectiveness below 2 years of age have not been established. A higher frequency of liver enzyme elevations and phototoxicity reactions has been observed in the paediatric population; hepatic function should be monitored, and stringent photoprotection measures are warranted.

4.5 Interaction with other medicinal products and other forms of interaction

Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and voriconazole (a strong CYP3A4 inhibitor) has the potential to increase plasma concentrations of substances metabolised by these isoenzymes.

Contraindicated combinations are listed in section 4.3. Combinations requiring dose adjustment or careful monitoring include:

Phenytoin (CYP2C9 substrate, potent CYP450 inducer): Concomitant use should be avoided unless benefit outweighs risk; if co-administered, voriconazole maintenance dose should be increased and phenytoin levels carefully monitored.

Ritonavir, low dose (100 mg twice daily): Should be avoided unless an assessment of benefit/risk justifies use.

Fluconazole: Co-administration significantly increases voriconazole Cmax and AUC; monitoring for voriconazole-associated adverse events is recommended if used sequentially.

Efavirenz (lower doses): Voriconazole maintenance dose should be increased to 400 mg every 12 hours, and efavirenz dose decreased to 300 mg once daily.

Everolimus, glasdegib, tyrosine kinase inhibitors (CYP3A4 substrates): Co-administration not recommended or requires dose reduction and close monitoring due to expected increases in plasma concentrations.

Methadone: Increased plasma concentrations associated with toxicity, including QT prolongation; frequent monitoring and dose reduction may be needed.

Short- and long-acting opiates (e.g. alfentanil, fentanyl, oxycodone, hydrocodone): Dose reduction should be considered with frequent monitoring for opiate-associated adverse events.

Ciclosporin and tacrolimus: Recommended that ciclosporin dose be halved, or tacrolimus dose reduced to one-third, with careful level monitoring, when initiating voriconazole; levels must be re-monitored and doses adjusted when voriconazole is discontinued.

Anticoagulants (warfarin and other coumarins): Voriconazole may increase prothrombin time; close monitoring and anticoagulant dose adjustment recommended.

Benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam): Increased plasma concentrations and prolonged sedative effect; dose reduction should be considered.

NSAIDs (e.g. ibuprofen, diclofenac): Increased plasma concentrations; frequent monitoring for NSAID-related adverse events and dose reduction may be needed.

Omeprazole and other CYP2C19-substrate proton pump inhibitors: Voriconazole increases omeprazole exposure; omeprazole dose should be halved when initiating voriconazole in patients on doses of 40 mg or above.

Oral contraceptives: Co-administration increases plasma concentrations of both ethinylestradiol/norethisterone and voriconazole; monitoring for adverse events related to both is recommended.

Letermovir and flucloxacillin: May significantly decrease voriconazole plasma concentrations; monitor for loss of efficacy if concomitant use cannot be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of voriconazole in pregnant women. Voriconazole should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether voriconazole is excreted in human milk. Breast-feeding should be discontinued at the start of treatment unless considered essential.

Fertility

No specific human fertility data are available.

4.7 Effects on ability to drive and use machines

Voriconazole may cause visual disturbances, including blurred vision, altered/enhanced visual perception, and/or photophobia. Patients

should avoid engaging in potentially hazardous tasks such as driving or operating machinery while experiencing these symptoms.

4.8 Undesirable effects

The most frequently reported adverse reactions (all causalities) in therapeutic trials were visual disturbances (approximately 18.7%), fever, nausea, rash, vomiting, chills, headache, liver function test abnormal, tachycardia, and hallucinations. The treatment-related adverse events which most often led to discontinuation were elevated liver function tests, rash, and visual disturbances.

Visual disturbances: Treatment-related visual disturbances are common; approximately 21% of patients experienced abnormal vision, colour vision change and/or photophobia in therapeutic trials. These are generally mild, transient and reversible, and rarely lead to discontinuation.

Skin reactions: Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported and can be life-threatening or fatal. Erythema multiforme has also been reported. Photosensitivity-related skin reactions, including pseudoporphyria, cheilitis, and cutaneous lupus erythematosus, have occurred.

Hepatic adverse reactions: Elevated ALT, abnormal liver function tests, and jaundice have accounted for a significant proportion of treatment discontinuations.

Other commonly reported adverse events include peripheral oedema, abdominal pain, respiratory disorder, sepsis, and diarrhoea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS):

https://pv.pharmacyboardkenya.org

4.9 Overdose

There is no known antidote to voriconazole. Voriconazole is haemodialysed with a clearance of 121 mL/min. In an overdose,

haemodialysis may assist in the removal of voriconazole from the body. Management of overdose should include symptomatic and supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives.

ATC code: J02AC03.

Voriconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has demonstrated fungicidal activity against Aspergillus species and fungistatic activity against yeasts.

5.2 Pharmacokinetic properties

Absorption

Voriconazole is rapidly and almost completely absorbed after oral administration, with maximum plasma concentrations (Cmax) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%. When voriconazole is taken with high-fat meals, Cmax and AUCτ are reduced by 34% and 24%, respectively; voriconazole should therefore be taken at least one hour before or after a meal.

Distribution

The volume of distribution at steady state is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%.

Biotransformation

In vitro studies showed that voriconazole is metabolised by the hepatic cytochrome P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4. The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism, with interindividual variability being high. CYP2C19 is

significantly polymorphic; poor metabolisers may have exposures approximately 4-fold higher than extensive metabolisers.

Elimination

Voriconazole is eliminated via hepatic metabolism, with less than 2% of the dose excreted unchanged in the urine. Due to non-linear pharmacokinetics, the terminal half-life is not useful in predicting accumulation or elimination.

5.3 Preclinical safety data

Non-clinical data indicate effects on the liver, adrenal cortex and reproductive systems in repeated-dose toxicity studies in animals, generally consistent with an exaggerated pharmacological effect or induction of hepatic enzymes. Voriconazole was not genotoxic in a standard battery of assays. Effects on reproductive organs and skeletal effects (delayed ossification, attributable to maternal toxicity) were observed in animal reproductive toxicity studies, and voriconazole was found to be teratogenic in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package to protect from moisture.

6.5 Nature and contents of container

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Unisel Pharma (K) Ltd,

Nairobi, Kenya.

8. Marketing Authorization Number

H2022/CTD10434/23905

9. Date of registration

10. Date of revision of the text

04 September 2026