Approved Professional Information for ZENOXPAR 600 mg

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZENOXPAR 600 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg linezolid.

Excipients with known effect:

Each tablet contains 0,82 mg soya lecithin.

For the full list of excipients, see section 6.1.

Sugar free.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oval shaped, biconvex film-coated tablets, debossed with “EQ1” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZENOXPAR formulations are indicated for the treatment of patients with the following infections caused by susceptible strains of the designated microorganisms.

ZENOXPAR is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy must be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see section 4.4).

- Vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteraemia.
- Nosocomial pneumonia, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multidrug-resistant *S. pneumoniae* (MDRSP) strains).
- Community-acquired pneumonia, caused by *Streptococcus pneumoniae* (including multidrug-resistant *S. pneumoniae* (MDRSP) strains), including cases with concurrent bacteraemia, or *Staphylococcus aureus* methicillin-susceptible and -resistant strains).

Due to concern about inappropriate use of antibiotics leading to an increase in resistant organisms, health care practitioners should carefully consider alternatives before starting treatment with **ZENOXPAR** in the outpatient setting.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to **ZENOXPAR**. Therapy may be instituted empirically while awaiting results of these tests. Antimicrobial therapy should be adjusted accordingly, once these results become available.

Prescribers should adhere to the principles of antibiotic stewardship.

4.2 Posology and method of administration

Posology

ZENOXPAR tablets may be used as initial therapy.

ZENOXPAR may be taken with or without food.

The recommended dosage for **ZENOXPAR 600 mg** is described below:

Adult and adolescent (12 years and older) patients

Infections (including those associated with concurrent bacteraemia)	**Dosage and route of administration**	**Duration of treatment**
Community-acquired pneumonia, including concurrent bacteraemia	600 mg orally every 12 hours	10 – 14 consecutive days
Nosocomial pneumonia, including concurrent bacteraemia		
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg orally every 12 hours	14 – 28 consecutive days

Special populations

Elderly patients

No dosage adjustment of **ZENOXPAR** is necessary.

Patients with renal insufficiency

No dosage adjustment of **ZENOXPAR** is necessary (see section 5.2).

Patients with severe renal insufficiency (i.e. Cr_{CR} < 30 mL/min)

No dose adjustment is required. Due to the unknown clinical significance of higher exposure (up to 10-fold) to the two primary metabolites of **ZENOXPAR** in patients with severe renal insufficiency, **ZENOXPAR** should be used with special caution in these patients.

As approximately 30 % of a **ZENOXPAR** dose is removed during 3 hours of haemodialysis, **ZENOXPAR** should be given after dialysis in patients receiving such treatment. The primary metabolites of **ZENOXPAR** are removed to some extent by haemodialysis, but the concentrations of these metabolites are still considerably higher following dialysis, than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Therefore, **ZENOXPAR** should be used with special caution in patients with severe renal insufficiency who are undergoing dialysis.

To date, there is no experience of **ZENOXPAR** administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than haemodialysis).

Patients with hepatic insufficiency

No dose adjustment is required. However, there are limited clinical data and it is recommended that **ZENOXPAR** should be used with special caution in such patients.

Paediatric population

ZENOXPAR is not suitable for children under 12 years of age.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, linezolid, or to any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Monoamine oxidase inhibitors, **ZENOXPAR** should not be used in patients taking any medicine which inhibits monoamine oxidases (e.g. phenelzine, isocarboxazid) or within two weeks of taking any such medicine.
- Potential interactions producing elevation of blood pressure, **ZENOXPAR** should not be administered to patients with uncontrolled hypertension, pheochromocytoma, hyperthyroidism and/or patients taking any of the following types of medicines: directly and indirectly acting sympathomimetic medicines (e.g. pseudoephedrine, phenylpropanolamine), vasopressive medicines (e.g. epinephrine (adrenaline), norepinephrine (noradrenaline)), dopaminergic medicines (e.g. dopamine, dobutamine) (see section 4.5).
- Potential serotonergic interactions, **ZENOXPAR** should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medicines: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine or buspirone (see section 4.5).

4.4 Special warnings and precautions for use

Myelosuppression

Reversible myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pre-treatment levels. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with linezolid may be at greater risk of experiencing blood dyscrasias than younger patients.

Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis. Therefore, close monitoring of blood counts is recommended in patients who have pre-existing anaemia, granulocytopenia or thrombocytopenia, receiving concomitant medicines that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function, have severe renal insufficiency and receive more than 10 – 14 days of therapy. Linezolid should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible.

If significant myelosuppression occurs during linezolid therapy, treatment should be stopped, unless it is considered absolutely necessary to continue therapy, in which case intensive monitoring of blood counts and appropriate management strategies should be implemented.

In addition, it is recommended that complete blood counts (including haemoglobin levels, platelets, total and differentiated leucocyte counts) should be monitored weekly in patients who receive linezolid regardless of baseline blood count.

In compassionate use studies, a higher incidence of serious anaemia was reported in patients receiving linezolid for more than the maximum recommended duration of 28 days. These patients more often required blood transfusion. Cases of anaemia requiring blood transfusion have also been reported post-marketing, with more cases occurring in patients who received linezolid therapy for more than 28 days.

Cases of sideroblastic anaemia have been reported post-marketing. Where time of onset was known, most patients had received linezolid therapy for more than 28 days. Most patients fully or partially recovered following discontinuation of linezolid with or without treatment for their anaemia.

Mortality imbalance in a clinical trial in patients with catheter-related Gram-positive bloodstream infections

ZENOXPAR has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected. **ZENOXPAR** should be used with special caution in patients at high risk for life threatening systemic infections, such as those with infections related to central venous catheters in intensive care units. **ZENOXPAR** is not approved for the treatment of patients with catheter-related bloodstream infections. The use of antibiotics may result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

The safety and effectiveness of **ZENOXPAR** when administered for periods longer than 28 days have not been established.

Antibiotic-associated diarrhoea and colitis

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea (CDAD), has been reported in association with the use of nearly all antibiotics, including linezolid, and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of linezolid. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial medicines, including linezolid, should be discontinued and adequate therapeutic measures should be initiated immediately. Medicines inhibiting peristalsis are contraindicated in this situation.

Treatment with **ZENOXPAR** alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines.

Lactic acidosis

Lactic acidosis has been reported with the use of linezolid. Patients who develop signs and symptoms of metabolic acidosis, including recurrent nausea or vomiting, abdominal pain, a low bicarbonate level, or hyperventilation while receiving linezolid, should receive immediate medical attention. If lactic acidosis occurs, discontinuation of **ZENOXPAR** should be considered.

Mitochondrial dysfunction

Linezolid inhibits mitochondrial protein synthesis. Adverse events, such as lactic acidosis, anaemia and neuropathy (optic and peripheral), may occur as a result of this inhibition, these events are more common when the medicines are used longer than 28 days.

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Co-administration of linezolid and serotonergic medicines is therefore contraindicated (see section 4.3), except where administration of linezolid and concomitant serotonergic medicines is essential. In those cases, patients should be closely observed for signs and symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur, medical practitioners should consider discontinuing either one or both medicines. If the concomitant serotonergic medicine is withdrawn, discontinuation symptoms can occur.

Rhabdomyolysis

Rhabdomyolysis has been reported with the use of linezolid. **ZENOXPAR** should be used with caution in patients with pre-disposing factors for rhabdomyolysis. If signs or symptoms of rhabdomyolysis are observed, linezolid should be discontinued and appropriate therapy initiated.

Hyponatraemia and SIADH

Hyponatraemia and/or syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been observed in some patients treated with linezolid. It is recommended that serum sodium levels are monitored regularly in patients at risk of hyponatraemia such as elderly patients or patients taking medicines that may lower blood sodium levels (e.g. thiazide diuretics such as hydrochlorothiazide).

Peripheral and optic neuropathy

Peripheral neuropathy, as well as optic neuropathy and optic neuritis, sometimes progressing to loss of vision, have been reported in patients treated with linezolid. These reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days.

All patients should be advised to report symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision or visual field defect. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary. If any patients are taking linezolid for longer than the recommended 28 days, their visual function should be regularly monitored.

If peripheral or optic neuropathy occurs, discontinuation of **ZENOXPAR** should be considered.

There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medicines for the treatment of tuberculosis.

Convulsions

Convulsions have been reported to occur in patients when treated with linezolid. In most of these cases, a history of seizures or risk factors for seizures was reported. Patients should be advised to inform their medical practitioner if they have a history of seizures.

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI) however, at the doses used for antibacterial therapy, it does not exert an anti-depressive effect. There are very limited data from medicine interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medicines which might put them at risk from MAO

inhibition. Therefore, linezolid is not recommended for use in these circumstances (see sections 4.3 and 4.5).

Use with tyramine-rich foods

Patients should be advised against consuming large amounts of tyramine-rich foods (see section 4.5).

Superinfection

The effects of linezolid therapy on normal flora have not been evaluated in clinical trials. The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. For example, approximately 3 % of patients receiving the recommended linezolid doses experienced medicines-related candidiasis during clinical trials. Should superinfection occur during therapy, appropriate measures should be taken.

Special populations

Linezolid should be used with special caution in patients with severe renal insufficiency (see sections 4.2 and 5.2). It is recommended that linezolid should be given to patients with severe hepatic insufficiency with caution (see sections 4.2 and 5.2).

Impairment of fertility

Linezolid reversibly decreased fertility and induced abnormal sperm morphology in adult male rats at exposure levels approximately equal to those expected in humans. Possible effects of linezolid on the human male reproductive system are not known.

Clinical trials

The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established. Controlled clinical trials did not include patients with diabetic foot lesions, decubitus

or ischaemic lesions, severe burns or gangrene. Therefore, experience in the use of linezolid in the treatment of these conditions is limited.

ZENOXPAR has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome or untreated hyperthyroidism.

ZENOXPAR should be used with special caution in patients with severe renal insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk.

ZENOXPAR contains soya lecithin

ZENOXPAR may contain traces of soy protein. If you are allergic to soya do not use this medicine.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI). Clinical studies have shown that it produces a mild, reversible enhancement of the pressor responses induced by pseudoephedrine and phenylpropanolamine hydrochloride. Thus, the potential for interaction with sympathomimetic or adrenergic medicines should be considered and doses of compounds, such as dopamine or adrenalin, should be titrated to achieve the desired response

There are very limited data from medicine interaction studies and on the safety of linezolid when administered to patients on concomitant medicines that might put them at risk from MAO inhibition, therefore, linezolid is not recommended for use in these circumstances (see sections 4.3 and 4.4).

Potential interactions producing elevation of blood pressure

In normotensive healthy volunteers, linezolid enhanced the increases in blood pressure caused by pseudoephedrine and phenylpropanolamine hydrochloride. Co-administration of linezolid with either pseudoephedrine or phenylpropanolamine resulted in mean increases in systolic blood pressure of the order of 30 – 40 mmHg, compared with 11 – 15 mmHg increases with linezolid alone, 14 –18 mmHg with either pseudoephedrine or phenylpropanolamine alone and 8 –11 mmHg with placebo. Similar studies in hypertensive subjects have not been conducted.

It is recommended that doses of medicines with a vasopressive action, including dopaminergic medicines, should be carefully titrated to achieve the desired response when co-administered with linezolid.

Potential serotonergic interactions

The potential interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20 mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

Post-marketing experience, there has been one report of a patient experiencing serotonin syndrome-like effects while taking linezolid and dextromethorphan which resolved on discontinuation of both medicines.

During clinical use of linezolid with serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), cases of serotonin syndrome have been reported. Therefore, while co-administration is contraindicated (see section 4.3), management of patients for whom treatment with linezolid and serotonergic medicines is essential, is described in section 4.4.

Use with tyramine-rich foods

No significant pressor response was observed in subjects receiving both linezolid and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting excessive amounts of food and beverages with a high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

Medicines metabolised by cytochrome P450

Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450-induced medicine interactions are expected with linezolid. Medicines such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with **ZENOXPAR** without changes in dosage regimen.

Rifampicin

The effect of rifampicin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2,5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased the linezolid C_{max} and AUC by a mean 21 % [90 % CI, 15, 27] and a mean 32 % [90 % CI, 27, 37], respectively. The mechanism of this interaction and its clinical significance are unknown.

Warfarin

When warfarin was added to linezolid therapy at steady-state, there was a 10 % reduction in mean maximum INR on co-administration, with a 5 % reduction in AUC INR. There are insufficient data from patients who have received warfarin and linezolid to assess the clinical significance, if any, of these findings.

Antibiotics

The pharmacokinetics of **ZENOXPAR** were not altered when administered together with either aztreonam or gentamicin.

4.6 Fertility, pregnancy and lactation

The use of **ZENOXPAR** in pregnancy and lactation is contraindicated, as safety has not been demonstrated (see section 4.3).

Pregnancy

There are limited data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity. A potential risk for humans exists. **ZENOXPAR** is contraindicated during pregnancy (see section 4.3).

Breastfeeding

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration. **ZENOXPAR** is contraindicated during lactation (see section 4.3).

Fertility

In animal studies, linezolid caused a reduction in fertility.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or symptoms of visual impairment (as described in section 4.4 and 4.8) whilst receiving linezolid and should be advised not to drive or operate machinery if any of these symptoms occurs.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported medicine-related adverse events which led to discontinuation of treatment were headache, diarrhoea, nausea and vomiting. About 3 % of patients discontinued treatment because they experienced a medicine-related adverse event.

Additional adverse reactions reported from post-marketing experience are included in the table with frequency category 'Not known', since the actual frequency cannot be estimated from the available data.

Tabulated list of adverse reactions

The following undesirable effects have been observed and reported during treatment with linezolid. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Infections and infestations	Frequent	Candidiasis, oral candidiasis, vaginal candidiasis, fungal infections, moniliasis[+]
	Less frequent	Vaginitis, antibiotic-associated colitis, including pseudomembranous colitis* and *C difficile*
Blood and the lymphatic system disorders	Frequent	Anaemia*[†], thrombocytopenia*
	Less frequent	Leucopenia*, neutropenia, eosinophilia, pancytopenia*, sideroblastic
	Frequency unknown	Myelosuppression*

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Immune system disorders	Less frequent	Anaphylaxis
Metabolism and nutrition disorders	Less frequent	Hyponatraemia, Lactic acidosis*, increased serum creatine, phosphokinase, hyperglycaemia
Psychiatric disorders	Frequent	Insomnia
Nervous system disorders	Frequent	Headache, taste perversion (metallic taste), dizziness
	Less frequent	Convulsions*, hypoaesthesia, paraesthesia, peripheral neuropathy*
	Frequency unknown	Serotonin syndrome**
Eye disorders	Less frequent	Blurred vision*, changes in visual field defect*, optic neuropathy*
	Frequency unknown	Optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Dysrhythmia (tachycardia), hypotension
Vascular disorders	Frequent	Hypertension
	Less frequent	Transient ischaemic attacks
Gastrointestinal disorders	Frequent	Diarrhoea^{+}, nausea^{+}, vomiting^{+}, localised or general abdominal pain^{+}, constipation, dyspepsia, cramps^{+} or distension^{+}

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
	Less frequent	Pancreatitis, gastritis, dry mouth, glossitis, loose stools, increased thirst, stomatitis, tongue discoloration or disorder, superficial tooth discoloration
Hepato-biliary disorders	Frequent	Abnormal liver function test, increased AST, ALT or alkaline phosphatase
	Less frequent	Increased total bilirubin
Skin and subcutaneous tissue disorders	Frequent	Pruritus, rash
	Less frequent	Urticaria, dermatitis, diaphoresis, angioedema, bullous, Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity vasculitis
	Frequency unknown	Alopecia
Musculoskeletal and connective tissue disorder	Less frequent	Rhabdomyolysis*
Renal and urinary disorders	Frequent	Increased blood urea
	Less frequent	Renal failure, increased creatinine, polyuria
Reproductive system and breast disorders	Less frequent	Vulvovaginal disorder, polyuria, vaginitis
	Frequent	Fever, localised pain

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
General disorders and administration site conditions	Less frequent	Chills, fatigue, increased thirst, phlebitis/thrombophlebitis, localised pain
Investigations	Frequent	*Chemistry* Increased total bilirubin, AST, ALT, LDH, alkaline phosphatase, BUN, creatine kinase, lipase, amylase or non-fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate. *Haematology* Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.
	Less frequent	*Chemistry* Increased sodium or calcium. Decreased non-fasting glucose. Increased or decreased chloride. *Haematology* Increased reticulocyte count. Decreased neutrophils

*See section 4.4.

**See sections 4.3 and 4.5

† See below

+ Events considered medicine-related in controlled clinical trials with an incidence of at least 1 %.

The following adverse reactions to linezolid were considered to be serious in rare cases: localised abdominal pain, transient ischaemic attacks and hypertension.

†In controlled clinical trials where linezolid was administered for up to 28 days, 2,0 % of the patients reported anaemia. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia when receiving linezolid for ≤ 28 days was 2,5 % (33/1326) as compared with 12,3 % (53/430) when treated for > 28 days. The proportion of cases reporting medicine-related serious anaemia and requiring blood transfusion was 9 % (3/33) in patients treated for ≤ 28 days and 15 % (8/53) in those treated for > 28 days.

Paediatric population

Safety data from clinical studies based on more than 500 paediatric patients (from birth to 17 years) do not indicate that the safety profile of linezolid for paediatric patients differs from that for adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **ZENOXPAR** is important. It allows continued monitoring of the benefit/risk balance of **ZENOXPAR**. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Side effects may be elicited and/or exacerbated.

Supportive care is advised together with maintenance of glomerular filtration. Approximately 30 % of a linezolid dose is removed during 3 hours of haemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotic.

Pharmacotherapeutic group: Antibacterials for systemic use; Other antibacterials.

ATC Code: J01XX08.

Mechanism of action

Linezolid is a synthetic, antibacterial medicine that belongs to a new class of antimicrobials, the oxazolidinones. It has *in vitro* activity against aerobic Gram-positive bacteria and anaerobic micro-organisms. Linezolid selectively inhibits bacterial protein synthesis via a unique mechanism of action. Specifically, it binds to a site on the bacterial ribosome (23S of the 50S subunit) and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process.

Resistance

Linezolid's mechanism of action differs from that of other antibiotics (e.g. the aminoglycosides, beta-lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifamycins, streptogramins, tetracyclines and chloramphenicol).

Therefore, there is no cross-resistance between linezolid and these classes of medicines.

In vitro studies have shown that resistance to linezolid develops slowly via multiple step mutations in 23S ribosomal RNA and occurs at frequencies of less than 1×10^{-9} to 1×10^{-11}.

5.2 Pharmacokinetic properties

ZENOXPAR primarily contains linezolid that is biologically active and is metabolised to form inactive metabolites.

Absorption

Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing. Absolute oral bioavailability of linezolid is complete (approximately 100 %). Absorption is not significantly affected by food.

Distribution

Volume of distribution at steady-state averages at about 40 – 50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31 % and is not concentration dependent.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in volunteer studies following multiple dosing. The ratio of linezolid in saliva and sweat relative to plasma was 1,2:1,0 and 0,55:1,0, respectively. The ratio for epithelial lining fluid and alveolar cells of the lung was 4,5:1,0 and 0,15:1,0, when measured at steady-state C_{max}, respectively.

In a small study of subjects with ventricular-peritoneal shunts and essentially non- inflamed meninges, the ratio of linezolid in cerebrospinal fluid to plasma at C_{max} was 0,7:1,0 after multiple linezolid dosing.

Biotransformation

Linezolid is primarily metabolised by oxidation of the morpholine ring resulting mainly in the formation of two inactive open-ring carboxylic acid derivatives; the aminoethoxyacetic acid metabolite (PNU-142300) and the hydroxyethyl glycine metabolite (PNU-142586). The hydroxyethyl glycine metabolite (PNU-142586) is the predominant human metabolite and is believed to be formed by a non-enzymatic

process. The aminoethoxyacetic acid metabolite (PNU142300) is less abundant. Other minor, inactive metabolites have been characterised.

Elimination

In patients with normal renal function or mild to moderate renal insufficiency, linezolid is primarily excreted under steady-state conditions in the urine as PNU-142586 (40 %), parent medicine (30 %) and PNU-142300 (10 %). Virtually no parent medicine is found in the faeces whilst approximately 6 % and 3 % of each dose appears as PNU-142586 and PNU142300, respectively. The elimination half-life of linezolid averages at about 5 – 7 hours.

Non-renal clearance accounts for approximately 65 % of the total clearance of linezolid. A small degree of non-linearity in clearance is observed with increasing doses of linezolid. This appears to be due to lower renal and non-renal clearance at higher linezolid concentrations. However, the difference in clearance is small and is not reflected in the apparent elimination half-life.

Special populations

Renal impairment

No dose adjustment is necessary in patients with either mild, moderate or severe renal insufficiency, as linezolid clearance is independent of creatinine clearance.

After single doses of 600 mg, there was a 7 – 8-fold increase in exposure to the two primary metabolites of linezolid in the plasma of patients with severe renal insufficiency (i.e. creatinine clearance < 30 mL/min).

As approximately 30 % of a dose is removed during 3 hours of haemodialysis (beginning 3 hours after administration), linezolid should be given after dialysis in patients receiving such treatment.

However, there was no increase in AUC of parent medicine. Although there is some removal of the major metabolites of linezolid by haemodialysis, metabolite plasma levels after single 600 mg doses

were still considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Hepatic impairment

The pharmacokinetics of linezolid are not altered in patients with mild to moderate hepatic insufficiency. Dose adjustment in such patients is, therefore, not required. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency has not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

Paediatric population (< 18 years old)

The pharmacokinetics of linezolid following a single IV dose were investigated in paediatric patients ranging in age from birth through 17 years (including premature and full-term neonates).

In adolescents (12 – 17 years of age), linezolid pharmacokinetics were similar to that in adults following a 600 mg dose.

The C_{max} and the volume of distribution (V_{ss}) are similar regardless of age in paediatric patients. However, clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from > 1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of paediatric patients increases the clearance of linezolid gradually decreases and by adolescence mean clearance values approach these observed for the adult population. There is wider inter-subject variability in linezolid clearance and systemic medicine exposure (AUC) across all paediatric age groups as compared with adults.

Elderly

The pharmacokinetics of linezolid are not significantly altered in elderly patients aged 65 and over.

Female patients

Females have a slightly lower volume of distribution than males and the mean clearance is reduced by approximately 20 % when corrected for body weight. Plasma concentrations are higher in females and this can partly be attributed to body weight differences. However, because the mean half-life of linezolid is not significantly different in males and females, plasma concentrations in females are not expected to substantially rise above those known to be well tolerated and, therefore, dose adjustments are not required.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate

Microcrystalline cellulose

Hydroxypropyl cellulose (hyprolose)

Sodium starch glycolate (Type A).

Film coating

Opadry White, consisting of:

Polyvinyl alcohol (E1203)

Titanium dioxide (E171)

Talc (E553b)

Soya lecithin (E322)

Xanthan gum (E415).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Alu-Alu blister packs comprising lidding foil made of hard tempered aluminium foil with HSL coating on bright side and cold formable, triple laminated aluminium foil as forming foil.

Blisters are packed in a carton along with package leaflet.

Or

Wide mouth white opaque HDPE container fitted with white opaque polypropylene child resistant closure or continuous thread screw closure (with wad having induction sealing liner) and a desiccant disc.

Pack sizes:

Each box of Alu-Alu blister contains 1, 10, 20, 30, 50, 60 or 100 tablets.

Each HDPE bottle contains 10, 30, 100 or 500 tablets.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Limited

Building 2, Tuscany Office Park

6 Coombe Place

Rivonia

Johannesburg

South Africa

Tel: (+27) 11 234 5701/2

Email: ra@accordhealth.co.za

8. REGISTRATION NUMBER

52/20.1.1/1006

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 April 2021

Date of latest renewal: To be allocated.

10. DATE OF REVISION OF THE TEXT

20 July 2026.