

1. NAME OF THE MEDICINAL PRODUCT

Linezolid Sandoz® Film-Coated Tablets 600mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of linezolid.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off white colored biconvex oval shaped film-coated tablet with “LZ600” debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Linezolid formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms. Linezolid is active against Gram-positive bacteria only. Linezolid has no clinical activity against Gram-negative pathogens. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected (See sections 4.4 and 5.1).

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

Complicated skin and skin structure infections including diabetic foot infections, without concomitant osteomyelitis caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Linezolid has not been studied in the treatment of decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*.

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

Due to concerns about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with linezolid 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 linezolid. Therapy may be instituted empirically while awaiting the results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

4.2 Posology and method of administration

Patients whose therapy is started with linezolid injection may be switched to linezolid tablets or linezolid for oral suspension, with no dosage adjustment.

Table 1. Dosage Guidelines for Linezolid

Infection*	Dosage and Route of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients † (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Complicated skin and skin structure infections	10 mg/kg IV or oral ‡ q8h	600 mg IV or oral ‡ q12h	10 to 14
Community-acquired pneumonia, including concurrent bacteremia			
Nosocomial pneumonia			
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg IV or oral ‡ q8h	600 mg IV or oral ‡ q12h	14 to 28
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral ‡ q8h 5-11 yrs: 10 mg/kg oral ‡ q12h	Adults: 400 mg oral ‡ q12h Adolescents: 600 mg oral ‡ q12h	10 to 14

* Due to the designated pathogens

† **Neonates <7 days:** Most pre-term neonates <7 days of age (gestational age <34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life.

‡ Oral dosing using either Linezolid Tablets or Linezolid for Oral Suspension.

Elderly patients: No dose adjustment is required.

Patients with renal insufficiency: No dose adjustment is required (see section 5.2).

Patients with severe renal insufficiency (i.e., CL_{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 linezolid in patients with severe renal insufficiency, linezolid should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

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

Therefore, linezolid should be used with special caution in patients with severe renal insufficiency who are undergoing dialysis and only when the anticipated benefit is considered to outweigh the theoretical risk.

To date, there is no experience of linezolid administration to patients undergoing continuous ambulatory

peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than hemodialysis).

Patients with hepatic insufficiency: No dose adjustment is required. However, there are limited clinical data and it is recommended that linezolid should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk (see section 5.2).

Method of administration:

The recommended linezolid dosage should be administered orally twice daily.

Route of administration: Oral use.

The film-coated tablets may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks of taking any such medicinal product.

Unless there are facilities available for close observation and monitoring of blood pressure, linezolid should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant medications:

- Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
- Patients taking any of the following medications: serotonin re-uptake inhibitors (see section 4.4), tricyclic antidepressants, serotonin 5-HT₁ receptor agonists (triptans), directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration (see section 4.6).

4.4 Special warnings and precautions for use

Myelosuppression

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 pretreatment 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; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; 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, and 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 patients with catheter-related Gram-positive bloodstream infections

Excess mortality was seen in patients treated with linezolid, relative to vancomycin/dicloxacillin/oxacillin, in seriously ill patients with intravascular catheter-related infections. Therefore, in complicated skin and soft tissue infections linezolid should only be used in patients with known or possible co-infection with Gram negative organisms if there are no alternative treatment options available (see section 4.1). In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

Antibiotic-associated diarrhoea and colitis

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, 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 agents, including linezolid, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

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, the benefits of continued use of linezolid should be weighed against the potential risks.

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 drug is used longer than 28 days.

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Co-administration of linezolid and serotonergic agents is therefore contraindicated (see section 4.3) except where administration of linezolid and concomitant serotonergic agents 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 physicians should consider discontinuing either one or both agents; if the concomitant serotonergic agent is withdrawn, discontinuation symptoms can occur.

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, the continued use of linezolid should be weighed against the potential risks.

There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medications 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 physician 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 drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (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 drug-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 and only when the anticipated benefit is considered to outweigh the theoretical risk (see sections 4.2 and 5.2).

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk (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 (see section 5.3).

Clinical trials

The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established. Experience in the use of linezolid in the treatment of patients with diabetic foot lesions, decubitus or ischaemic lesions, severe burns or gangrene is limited.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI). There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients on concomitant medications that might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (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 drugs with a vasopressive action, including dopaminergic agents, should be carefully titrated to achieve the desired response when co-administered with linezolid.

Potential serotonergic interactions

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 medications.

During clinical use of linezolid with serotonergic agents, 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 agents 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).

Drugs 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 drug interactions are expected with linezolid.

Rifampicin

Rifampicin decreased the linezolid C_{max} and AUC. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). A potential risk for humans exists.

Linezolid should not be used during pregnancy unless clearly necessary i.e. only if the potential benefit outweighs the theoretical risk.

Breast-feeding

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breast-feeding should be discontinued prior to and throughout administration.

Fertility

In animal studies, linezolid caused a reduction in fertility (see section 5.3).

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

The most commonly reported drug-related adverse events, which led to discontinuation of treatment, were

headache, diarrhea, nausea and vomiting. The following undesirable effects have been observed and reported during treatment with linezolid with the following frequencies: Very common; common; uncommon; rare; very rare; Not known.

System Organ Class	Frequency	Events
Infections and infestations	Common	Candidiasis, oral candidiasis, vaginal candidiasis, fungal infections
	Uncommon	Vaginitis
	Rare	Antibiotic-associated colitis, including pseudo-membranous colitis*
Blood and the Lymphatic system disorders	Common	Anaemia*
	Uncommon	Leucopenia*, neutropenia, thrombocytopenia*, eosinophilia
	Rare	Pancytopenia*
	Frequency not known	Myelosuppression*, sideroblastic anaemia*
Immune system disorders	Frequency not known	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Hyponatraemia
	Frequency not known	Lactic acidosis*
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Common	Headache, taste perversion (metallic taste), dizziness
	Uncommon	Convulsion*, hyposaesthesia, paraesthesia
	Frequency not known	Serotonin syndrome**, peripheral neuropathy*
Eye disorders	Uncommon	Blurred vision*
	Rare	Changes in visual field defect*
	Frequency not known	Optic neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Arrhythmia (tachycardia)
Vascular disorders	Common	Hypertension
	Uncommon	Transient ischaemic attacks, phlebitis, thrombophlebitis
Gastrointestinal disorders	Common	Diarrhoea, nausea, vomiting, localised or general abdominal pain, constipation, dyspepsia
	Uncommon	Pancreatitis, gastritis, abdominal distention, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder
	Rare	Superficial tooth discolouration
Hepato-biliary disorders	Common	Abnormal liver function test; increased AST, ALT or alkaline phosphatase
	Uncommon	Increased total bilirubin
Skin and subcutaneous tissue disorders	Common	Pruritus, rash
	Uncommon	Urticaria, dermatitis, diaphoresis
	Frequency not known	Bullous disorders such as those described as Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, alopecia
Renal and urinary disorders	Common	Increased BUN
	Uncommon	Renal failure, increased creatinine, polyuria
Reproductive system and breast disorders	Uncommon	Vulvovaginal disorder
General disorders and administration site conditions	Common	Fever, localised pain
	Uncommon	Chills, fatigue, injection site pain, increased thirst
Investigations	Common	Chemistry: Increased LDH, 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.
	Uncommon	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

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

Paediatric population

Safety data from clinical studies based on 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.

4.9 Overdose

No specific antidote is known.

No cases of overdose have been reported. However, the following information may prove useful:

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. The two primary metabolites of linezolid are also removed to some extent by haemodialysis.

Signs of toxicity in rats following doses of 3000 mg/kg/day linezolid were decreased activity and ataxia whilst dogs treated with 2000 mg/kg/day experienced vomiting and tremors.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antibacterials. ATC code: J01XX08

General properties

Linezolid is a synthetic, antibacterial agent 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.

The in vitro postantibiotic effect (PAE) of linezolid for *Staphylococcus aureus* was approximately 2 hours. When measured in animal models, the in vivo PAE was 3.6 and 3.9 hours for *Staphylococcus aureus* and *Streptococcus pneumoniae*, respectively. In animal studies, the key pharmacodynamic parameter for efficacy was the time for which the linezolid plasma level exceeded the minimum inhibitory concentration (MIC) for the infecting organism.

Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and enterococci are Susceptible \leq 4mg/L and Resistant $>$ 4 mg/L. For streptococci (including *S. pneumoniae*) the breakpoints are Susceptible \leq 2 mg/L and Resistant $>$ 4 mg/L.

Non-species related MIC breakpoints are Susceptible \leq 2 mg/L and Resistant $>$ 4 mg/L. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that have not been given a specific breakpoint and not for those species where susceptibility testing is not recommended.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Category
<u>Susceptible organisms</u> Gram-positive aerobes: <i>Enterococcus faecalis</i> <i>Enterococcus faecium</i> * <i>Staphylococcus aureus</i> * Coagulase negative staphylococci <i>Streptococcus agalactiae</i> * <i>Streptococcus pneumoniae</i> * <i>Streptococcus pyogenes</i> * Group C streptococci Group G streptococci Gram-positive anaerobes: <i>Clostridium perfringens</i> <i>Peptostreptococcus anaerobius</i> <i>Peptostreptococcus species</i>
<u>Resistant organisms</u> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Neisseria species</i> Enterobacteriaceae <i>Pseudomonas species</i>

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

Whereas linezolid shows some in vitro activity against *Legionella*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, there are insufficient data to demonstrate clinical efficacy.

Resistance

Cross resistance

Linezolid's mechanism of action differs from those of other antibiotic classes. In vitro studies with clinical isolates (including methicillin-resistant staphylococci, vancomycin-resistant enterococci, and penicillin- and erythromycin-resistant streptococci) indicate that linezolid is usually active against organisms which are resistant to one or more other classes of antimicrobial agents.

Resistance to linezolid is associated with point mutations in the 23S rRNA.

As documented with other antibiotics when used in patients with difficult to treat infections and/or for prolonged periods, emergent decreases in susceptibility have been observed with linezolid. Resistance to linezolid has been reported in enterococci, *Staphylococcus aureus* and coagulase negative staphylococci. This generally has been associated with prolonged courses of therapy and the presence of prosthetic materials or undrained abscesses. When antibiotic-resistant organisms are encountered in the hospital it is important to emphasize infection control policies.

5.2 Pharmacokinetic properties

Linezolid Sandoz primarily contains (s)-linezolid which is biologically active and is metabolised to form inactive derivatives.

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 (oral and intravenous dosing in a crossover study) is complete (approximately 100%). Absorption is not significantly affected by food and absorption from the oral suspension is similar to that achieved with the film-coated tablets.

Plasma linezolid C_{max} and C_{min} (mean and [SD]) at steady-state following twice daily intravenous dosing of 600 mg have been determined to be 15.1 [2.5] mg/l and 3.68 [2.68] mg/l, respectively.

In another study following oral dosing of 600 mg twice daily to steady-state, C_{max} and C_{min} were determined to be 21.2 [5.8] mg/l and 6.15 [2.94] mg/l, respectively. Steady-state conditions are achieved by the second day of dosing.

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 (PNU-142300) 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 drug (30%) and PNU-142300 (10%). Virtually no parent drug is found in the faeces whilst approximately 6% and 3% of each dose appears as PNU-142586 and PNU-142300, 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

Patients with renal insufficiency

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). However, there was no increase in AUC of parent drug. 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.

In 24 patients with severe renal insufficiency, 21 of whom were on regular haemodialysis, peak plasma concentrations of the two major metabolites after several days dosing were about 10-fold those seen in patients with normal renal function. Peak plasma levels of linezolid were not affected.

The clinical significance of these observations has not been established as limited safety data are currently available (see sections 4.2 and 4.4).

Patients with hepatic insufficiency

Limited data indicate that the pharmacokinetics of linezolid, PNU-142300 and PNU-142586 are not altered in patients with mild to moderate hepatic insufficiency (i.e. Child-Pugh class A or B). The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (i.e. Child-Pugh class C) have 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 (see sections 4.2 and 4.4).

Children and adolescents (<18 years old)

There are insufficient data on the safety and efficacy of linezolid in children and adolescents (<18 years old) and therefore, use of linezolid in this age group is not recommended (see section 4.2). Further studies are needed to establish safe and effective dosage recommendations. Pharmacokinetic studies indicate that after single and multiple doses in children (1 week to 12 years), linezolid clearance (based on kg body weight) was greater in paediatric patients than in adults, but decreased with increasing age.

In children 1 week to 12 years old, administration of 10 mg/kg every 8 hours daily gave exposure approximating to that achieved with 600 mg twice daily in adults.

In neonates up to 1 week of age, the systemic clearance of linezolid (based on kg body weight) increases rapidly in the first week of life. Therefore, neonates given 10 mg/kg every 8 hours daily will have the greatest systemic exposure on the first day after delivery. However, excessive accumulation is not expected with this dosage regimen during the first week of life as clearance increases rapidly over that period.

In adolescents (12 to 17 years old), linezolid pharmacokinetics were similar to that in adults following a 600 mg dose. Therefore, adolescents administered 600 mg every 12 hours daily will have similar exposure to that observed in adults receiving the same dosage.

In paediatric patients with ventriculoperitoneal shunts who were administered linezolid 10 mg/kg either 12 hourly or 8 hourly, variable cerebrospinal fluid (CSF) linezolid concentrations were observed following either single or multiple dosing of linezolid. Therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empirical treatment of paediatric patients with central nervous system infections is not recommended.

Elderly patients

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

Excipients (core):

Cellulose microcrystalline
Silica colloidal anhydrous
Sodium starch glycolate type A
Hydroxypropyl cellulose
Magnesium stearate.

Excipients (coating):

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

10 tablets are packed in an Al/Al blister.

There are two pack sizes, 30 tablets (3x10s) and 100 tablets (10x10s) packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

Oct 2025