ZYVOX®
Linezolid

1. NAME OF THE MEDICINAL PRODUCT

ZYVOX Tablet 600 mg
ZYVOX Solution for Infusion 2 mg/ml
ZYVOX Granules for Oral Suspension 20 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablets : Each tablet contains 600 mg of linezolid.

Solution for infusion : Each ml contains 2 mg of linezolid.

Powder for oral suspension : Following constitution, each 5 ml contains 100 mg of linezolid.

For excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Film-coated tablets, solution for infusion, powder for oral suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Linezolid is indicated for the treatment of **adults and adolescents (12 years and older) and pediatric patients (birth through 11 years of age)** with the following infections caused by susceptible strains of Gram-positive bacteria only. Linezolid 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 (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

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

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant strains) or *Streptococcus pneumoniae* (penicillin-sensitive strains only).

Uncomplicated skin and soft tissue infections caused by *Staphylococcus aureus* (methicillin-sensitive strains only) or *Streptococcus pyogenes*.

Complicated skin and soft tissue infections, caused by *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant strains), *Streptococcus pyogenes* or *Streptococcus agalactiae*.

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

Linezolid should not be initiated as a first line therapy for community-acquired pneumonia or uncomplicated skin infection, but may be considered if resistant strains are suspected or proven or in presence of drug allergy.

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.

Dosing Recommendations for Adults and Adolescents (12 years old and older)		
Indication	**Dosage and Route of Administration**	**Recommended Duration of Treatment (consecutive days)**
Community-acquired pneumonia	600 mg IV or orally every 12 hours	10 – 14 days
Nosocomial pneumonia		
Uncomplicated skin and soft tissue infections	Adults: 400 mg orally every 12 hours Adolescents: 600 mg orally every 12 hours	10 – 14 days
Complicated skin and soft tissue infections	600 mg IV or orally every 12 hours	10 – 14 days
Vancomycin-resistant Enterococcus infections	600 mg IV or orally every 12 hours	14 – 28 days
Dosing Recommendations for Pediatric Patients (Birth* through 11 years of age)		
Indication	**Dosage and Route of Administration**	**Recommended Duration of Treatment (consecutive days)**
Community-acquired pneumonia	10 mg/kg IV or orally every 8 hours	10 – 14 days
Nosocomial pneumonia		
Uncomplicated skin and soft tissue infections	<5 yrs: 10 mg/kg orally every 8 hours 5-11 yrs: 10 mg/kg orally every 12 hours	10 – 14 days
Complicated skin and soft tissue infections	10 mg/kg IV or orally every 8 hours	10 – 14 days
Vancomycin-resistant Enterococcus infections	10 mg/kg IV or orally every 8 hours	14 – 28 days
Duration of treatment is variable, depending on the pathogen isolated, site of infection and its severity. To date the maximum duration of treatment has been 28 days. * Pre-term neonates less than 7 days of age (gestational age less than 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. By day 7 of age, linezolid clearance and AUC values are similar to those of full-term neonates and older infants.		

Elderly patients: No dose adjustment is required.

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

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 Pharmacokinetic properties).

Pediatric: Recommended dosages for pediatric patients please refer to the table above.

Linezolid Injection
Administer linezolid injection by intravenous infusion over a period of 30 to 120 minutes. **Do not use the intravenous infusion bag in series connections**. Do not introduce additives into the intravenous solution. If linezolid injection is to be given concomitantly with another drug, each drug should be given separately, in accordance with the recommended dosage and route of administration for each product.

Linezolid injection was physically incompatible with the following drugs when combined in simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, phenytoin sodium, erythromycin lactobionate and trimethoprim-sulfamethoxazole.

Linezolid injection was chemically incompatible when combined with ceftriaxone sodium.

Compatible Infusion Solutions:
5% Dextrose Injection
0.9% Sodium Chloride Injection
Lactated Ringer's Injection

4.3 Contraindications

Linezolid is contraindicated in patients who have previously demonstrated hypersensitivity to linezolid or any of the other product components.

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

Potential Interactions Producing Elevation of Blood Pressure
Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine, phenylpropanolamine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine) (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Potential Serotonergic Interactions
Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine or buspirone (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Pseudomembranous Colitis
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid, and may range in severity from mild to life-threatening.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including linezolid, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents 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 diarrhea following antibiotic use.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Myelosuppression
Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. Thrombocytopenia may occur more often in patients with severe renal insufficiency, whether or not on dialysis, and in patients with moderate to severe hepatic impairment. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those with severe renal insufficiency or moderate to severe hepatic impairment, those receiving concomitant drugs that produce bone marrow suppression, or those with chronic infection who have received previous or concomitant antibiotic therapy.

Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.

Lactic Acidosis
Lactic acidosis has been reported with the use of linezolid. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation.

Development of Drug-Resistant Bacteria
Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Peripheral and Optic Neuropathy
Peripheral and optic neuropathy have been reported in patients treated with linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration.

If symptoms of visual impairment appear, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. Visual function should be monitored in all patients taking linezolid for extended periods (greater than or equal to 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with linezolid. If peripheral or optic neuropathy occurs, the continued use of linezolid in these patients should be weighed against the potential risks.

Convulsions
Convulsions have been reported to occur rarely in patients when treated with linezolid. In most of these cases, a history of seizures or risk factors for seizures were reported.

Serotonin Syndrome
Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin re-uptake inhibitors (SSRIs) and opioids have been reported (see sections 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction).

Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, 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 discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed.

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

The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

Rhabdomyolysis
Rhabdomyolysis has been reported with the use of linezolid. If signs or symptoms of rhabdomyolysis are observed, linezolid should be discontinued and appropriate therapy initiated.

Hyponatremia and SIADH
Hyponatremia 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 be monitored regularly in the elderly, in patients taking diuretics, and in other patients at risk of hyponatremia.

Co-administration with Rifampin
In healthy volunteers, co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid C_{max} and a 32% decrease in linezolid AUC (see section 4.5 Interaction with other medicinal products and other forms of interaction). The clinical significance of this interaction is unknown.

Use in Gram-negative Pathogens
Linezolid 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. Linezolid 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. Linezolid is not approved for the treatment of patients with catheter-related bloodstream infections.

Clinical Trial in Catheter-related Gram-positive Bloodstream Infections
An open-label, randomized clinical trial was conducted in adult patients with catheter-related Gram-positive bloodstream infections comparing linezolid (600 mg q12h IV/PO) to vancomycin 1 g IV q12h or oxacillin 2 g IV q6h/dicloxacillin 500 mg PO q6h with a treatment duration of 7 to 28 days. The mortality rates in this study were 78/363 (21.5%) and 58/363 (16.0%) on linezolid and the comparator, respectively. Based on results from a logistic regression, the estimated odds ratio is 1.426 [95% CI 0.970, 2.098]. While causality has not been established, this observed imbalance occurred primarily in linezolid-treated patients in whom either Gram-negative pathogens, mixed Gram-negative and Gram-positive pathogens, or no pathogen were identified at baseline. Patients randomized to linezolid who had only a Gram-positive infection at baseline, including the subgroup of patients with Gram-positive bacteremia experienced a survival rate similar to the comparator.

Information for Patients
Patients should be advised that:
- ZYVOX may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- They should avoid consuming food with high tyramine content.
- They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants.
- They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants.
- They should inform their physician if they experience changes in vision.
- They should inform their physician if they have a history of seizures.

• Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs Metabolized by Cytochrome P450
Linezolid is not detectably metabolized by the cytochrome P450 (CYP) enzyme system and it does not induce or inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-induced drug interactions are expected with linezolid. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Antibiotics
The pharmacokinetics of linezolid were not altered when administered together with either aztreonam or gentamicin. The effect of rifampin 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 rifampin 600 mg once daily for 8 days. Rifampin 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 (see section 4.4 Special warnings and precautions for use).

Monoamine Oxidase Inhibition
Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic Agents
A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content (e.g., mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects. A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg q12h for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments.

Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2 to 3 hours after the second dose of PPA or PSE, and returned to baseline 2 to 3 hours after peak. The results of the PPA study follow, showing the mean (and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg (range: 20-52 mm Hg) and 38 mm Hg

(range: 18-79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively. Initial doses of adrenergic agents, such as dopamine or dopamine agonists, should be reduced and titrated to achieve the desired response.

Serotonergic Agents

The potential drug-drug 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, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan. The effects of other serotonin re-uptake inhibitors have not been studied. However, very rare spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic agents have been reported (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Reproductive studies performed in mice and rats treated with linezolid showed no evidence of teratogenic effects. Mild fetal toxicity was observed in mice only at maternally toxic dose levels. In rats, fetal toxicity was manifested as decreased fetal body weights and reduced ossification of sternebrae (which is often seen in association with decreased body weights). Reduced pup survival and mild maturational delays occurred in rats. When mated, these same pups showed evidence of a reversible, dose-related increase in pre-implantation loss. There are no adequate and well-controlled studies in pregnant women. Therefore, linezolid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Linezolid decreased the fertility of male rats.

Linezolid transferred into the breast milk of lactating laboratory rats. It is not known whether linezolid is excreted in human milk. Therefore, caution should be exercised when linezolid is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

The effect of linezolid on the ability to drive or operate machinery has not been systematically evaluated.

4.8 Undesirable effects

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
Infections and infestations		Moniliasis				

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Thrombocytopenia*, Anemia*	Pancytopenia*, Leucopenia*	Sideroblastic anemia*		
Immune system disorders				Anaphylaxis*		
Metabolism and nutrition disorders				Lactic acidosis*		
Nervous system disorders		Headache	Convulsions*, Peripheral neuropathy*, Taste alteration			
Eye disorders			Optic neuropathy*			
Gastrointestinal disorders		Vomiting, Diarrhea, Nausea, Abdominal pain including abdominal cramps	Abdominal cramps[#], Abdominal distension, Tongue discoloration*	Superficial tooth discoloration*		
Skin and subcutaneous tissue disorders		Rash*	Bullous skin disorders, Severe cutaneous adverse reactions, Angioedema*	Toxic epidermal necrolysis*[§], Stevens-Johnson syndrome*[§], Hypersensitivity vasculitis*		
Musculoskeletal and connective tissue disorders				Rhabdomyolysis*		
Investigations		Abnormal liver function tests	Abnormal hematology tests			

*ADR identified post-marketing

[§] ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3".

[#] The ADR Abdominal cramps is defined by MedDRA LLT and not by PT.

4.9 Overdose

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 hemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or hemoperfusion. The primary metabolites of linezolid are also removed by hemodialysis. 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 (ATC code): J01XX08

Mechanism of Action
Linezolid is a synthetic, antibacterial agent which belongs to a class of antibiotics called oxazolidinones, with *in vitro* activity against aerobic Gram-positive bacteria, certain Gram-negative bacteria and anaerobic microorganisms. It selectively inhibits bacterial protein synthesis via a unique mechanism of action. Linezolid 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 results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for majority of strains.

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 to 3.9 hours for *Staphylococcus aureus* and *Streptococcus pneumoniae*, respectively. In animal studies, the key pharmacodynamic parameter for efficacy was the time that the linezolid plasma levels exceeded the minimum inhibitory concentration (MIC) of the infecting organism. Linezolid was efficacious when plasma levels exceeded the MIC of the infecting organism for a minimum of 40% of the dosing interval.

Mechanism of Resistance
The major mechanism of resistance to linezolid appears to be a modification to 23S ribosomal RNA.

Linezolid's mechanism of action differs from that of other antibiotic classes (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 drug. Linezolid is active against pathogens that are susceptible or resistant to such antibiotics.

Clinical Efficacy Against Specific Pathogens
This list is provided based on clinical efficacy and pharmacokinetic/pharmacodynamic data from clinical studies. 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.

Susceptibility
Linezolid has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections, as described in the section 4.1 Therapeutic indications.

Aerobic and facultative Gram-positive microorganisms
Enterococcus faecium (vancomycin-resistant strains only)
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae

Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for linezolid. However, the safety and effectiveness of linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms
Enterococcus faecalis (including vancomycin-resistant strains)
Enterococcus faecium (vancomycin-susceptible strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Streptococcus pneumoniae (penicillin-resistant strains)
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms
Pasteurella multocida

Susceptibility Testing Interpretive Criteria (Breakpoints)
The CLSI interpretive criteria for susceptibility testing of linezolid are listed in the following table:

CLSI Susceptibility Interpretive Criteria								
Pathogen	**Minimal Inhibitory Concentration (µg/mL of Linezolid)**				**Disk[a] Diffusion Inhibition Zone (mm Diameter)**			
	S	**SDD**	**I**	**R**	**S**	**SDD**	**I**	**R**
Enterococcus spp.	≤2	-	4	≥8	≥23	-	21-22	≤20
Staphylococcus spp.	≤4	-	-	≥8	≥26	-	23-25	≤22
Streptococcus pneumoniae	≤2	-	-	-	≥21	-	-	-
Streptococcus spp. β-hemolytic group	≤2	-	-	-	≥21	-	-	-
Streptococcus spp. viridans group	≤2	-	-	-	≥21	-	-	-
Aerococcus spp.	≤2	-	-	-	-	-	-	-
Corynebacterium spp. (including *C. diphtheriae*) and related coryneform genera	≤2	-	-	-	-	-	-	-
Lactobacillus spp.	≤4	-	-	-	-	-	-	-
Sources: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*; CLSI document M100:ED[35] 2025. This document is updated annually and may be accessed at http://clsi-m100.com/. *Clinical and Laboratory Standards Institute. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria*. CLSI guideline M45ED3 2016. S = Susceptible. SDD = Susceptible dose-dependent. I = Intermediate. R = Resistant. [a] Disk content 30 µg.								

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Quality control microorganisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for susceptibility test quality control are not clinically significant.

Organisms and quality control ranges for linezolid to be utilized with CLSI methodology and susceptibility test interpretive criteria are listed in the following table:

Quality Control Ranges for Linezolid to be Used in Conjunction with CLSI Susceptibility Test Interpretive Criteria

Quality Control Strain	Minimal Inhibitory Concentration (µg/mL of Linezolid)	Disk Diffusion[a] Inhibition Zone (mm Diameter)
Streptococcus aureus ATCC® 25923	1-4	24-30
Streptococcus pneumoniae ATCC® 49619	0.25-2	25-34
Bacteroides fragilis ATCC® 25285	2-8	-
Bacteroides thetaiotaomicron ATCC® 29741	2-8	-
Clostridioides difficile ATCC® 700057	1-4	-
Eggerthella lenta ATCC® 43055	0.5-2	-

Source: Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing, CLSI document M100:ED[35] 2025.
[a] Disk content 30 µg.

5.2 Pharmacokinetic properties

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 liters 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.

Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or

maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended.

Metabolism

Linezolid is primarily metabolized 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 characterized.

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 feces while 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- to 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 hemodialysis, 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 hemodialysis, 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 section 4.2 Posology and method of administration).

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 metabolized by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism (see section 4.2 Posology and method of administration).

Children and adolescents (<18 years old): 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 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.

Elderly patients: The pharmacokinetics of linezolid are not significantly altered in elderly patients aged 65 years 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.

5.3 Preclinical safety data

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those expected in humans. In sexually mature animals these effects were reversible. The reversible effects on fertility were mediated by altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. The presence of abnormal sperm in the epididymis was accompanied by epithelial cell hypertrophy and hyperplasia. Epididymal hypertrophy was not observed in dogs treated for 1 month, although changes in the weights of prostate, testes and epididymis were apparent.

Sexually mature male rats showed slightly decreased fertility following oral treatment as juveniles throughout most of their period of sexual development (50 mg/kg/day from postnatal days 7 to 36, and 100 mg/kg/day from days 37 to 55), at exposures up to 1.7 times the mean AUC in pediatric patients aged 3 months to 11 years. Decreased fertility was not observed following shorter treatment periods *in utero* through the early neonatal period (gestation day 6 through postnatal day 5), neonatal exposure (postnatal days 5 to 21), or juvenile exposure (postnatal days 22 to 35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats following treatment on postnatal days 22 to 35.

Reproductive toxicity studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4 times or equivalent, respectively, to those expected in humans. The same linezolid concentrations caused maternal toxicity in mice and were related to increased embryo death including total litter loss, decreased fetal body weight and an exacerbation of the normal genetic predisposition to sternal variations in the strain of mice. In rats, slight maternal toxicity was noted at exposures lower than expected clinical exposures. Mild fetal toxicity, manifested as decreased fetal body weights, reduced ossification of sternebrae, reduced pup survival and

mild maturational delays were noted. When mated, these same pups showed evidence of a reversible dose-related increase in pre-implantation loss with a corresponding decrease in fertility.

Linezolid was also not teratogenic in rabbits when administered twice daily at total oral doses up to 15 mg/kg/day (0.06 times the clinical exposure, based on AUC). Maternal toxicity (clinical signs, reduced body weight gain and food consumption) occurred at 5 and 15 mg/kg/day, and reduced fetal body weight occurred at 15 mg/kg/day. Linezolid exposures were low due to the characteristic sensitivity of rabbits to antibiotics.

Linezolid and its metabolites are excreted into the milk of lactating rats and the concentrations observed were higher than those in maternal plasma.

Linezolid produced reversible myelosuppression in adult and juvenile rats and dogs.

In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was evident in 2 male rats administered Linezolid at 80 mg/kg/day for 6 months, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The nerve degeneration observed was microscopically comparable to a spontaneous unilateral optic nerve degeneration reported in aging rats and may be an exacerbation of a common background change.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets:	Microcrystalline Cellulose, Corn Starch, Sodium Starch Glycolate, Hydroxypropylcellulose, Magnesium Stearate, Purified Water, Carnauba Wax, Opadry White YS-1-18202-A.
Solution for Infusion:	Glucose Monohydrate, Sodium Citrate $2H_2O$, Citric Acid Anhydrous, Hydrochloric Acid, Sodium Hydroxide, Water for Injections.
Granules for Oral Suspension:	Sucrose Granular, Mannitol Powder, Microcrystalline Cellulose and Carboxymethylcellulose Sodium, Aspartame Powder, Sodium Citrate Hydrous Granular, Xanthan Gum, Sodium Benzoate, Citric Acid Anhydrous Powder, Colloidal Silicon Dioxide, Sodium Chloride, MAFCO Magnasweet #135, Orange flavour (Natural & Artificial), Orange cream flavour (Natural & Artificial), Sweet-AM powder #918.005, Vanilla flavour (Natural & Artificial), Peppermint flavour (Natural & Artificial), Purified Water.

6.2 Incompatibilities

Solution for Infusion:	Additives should not be introduced into this solution. If linezolid is to be given concomitantly with other drugs, each drug should be given separately in accordance with its own directions for use. Similarly, if the same intravenous line is to be used for sequential infusion of several drugs, the line should be flushed prior to and following linezolid administration with a compatible infusion solution (see section 6.6 Instructions for use and handling). ZYVOX solution for infusion is known to be physically incompatible with the following compounds: amphotericin B, chlorpromazine hydrochloride, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium and sulphamethoxazole/trimethoprim. Additionally, it is chemically incompatible with ceftriaxone sodium.

6.3 Shelf life

Please refer to outer carton for shelf-life.

6.4 Special precautions for storage

ZYVOX Tablet 600 mg:	Store below 30°C.
ZYVOX Solution for Infusion 2 mg/ml:	Store at 25°C; excursions permitted to 15°C - 30°C. Do not freeze. Keep bags in foil overwrap and carton until ready to use.
ZYVOX Granules for Oral Suspension 20 mg/ml:	Store at 25°C; excursions permitted to 15°C - 30°C. <u>Before reconstitution</u> Keep the bottle tightly closed. <u>After reconstitution</u> Keep the bottle in the outer carton.

6.5 Nature and contents of container

ZYVOX Tablet 600 mg:	Blister pack of 10's & 20's
ZYVOX Solution for Infusion 2 mg/ml:	600 mg/300 ml foil bag
ZYVOX Granules for Oral Suspension 20 mg/ml:	240 ml amber glass bottle (150 ml when constituted)

Not all presentations may be available locally.

6.6 Instructions for use and handling

Tablets: No special requirements.

Granules for Oral Suspension 20 mg/ml: Gently tap bottle to loosen powder. Add a total of 123 ml distilled water in two portions. After adding the first half, shake vigorously to wet all of the powder. Then add the second half of the water and shake vigorously to obtain a uniform suspension. Each 5 ml of oral suspension contains 100 mg linezolid. Before using, gently mix by inverting the bottle 3 to 5 times. DO NOT SHAKE. Keep container tightly closed. Protect from light and moisture. Store constituted suspension at room temperature. Discard unused portion after 21 days.

Solution for Infusion 2 mg/ml: Remove overwrap only when ready to use, then check for minute leaks by squeezing the bag firmly. If the bag leaks, do not use as sterility may be impaired. Do not use these bags in series connections. Any unused solution must be discarded. Do not reconnect partially used bags.

ZYVOX solution for infusion is compatible with the following solutions: 5% dextrose injection, 0.9% sodium chloride injection, Lactated Ringer's injection (Hartmann's solution for injection).

7. PRODUCT OWNER

Pfizer Inc.
New York,
United States

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