1. NAME OF THE MEDICINAL PRODUCT

ZYVOX®

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 5mL contains 100 mg of linezolid.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Linezolid solution for infusion is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each mL contains 2 mg of linezolid.

Linezolid tablets for oral administration contain 600 mg linezolid as film-coated compressed tablets.

Linezolid for Oral Suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration.

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).

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.

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

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.*

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

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 *Enterococcus faecium* 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).

Linezolid solution for infusion
Administer linezolid solution for infusion by intravenous infusion over a period of 30 to 120 minutes. **Do not use this intravenous infusion bag in series connections**. Do not introduce additives into the intravenous solution. If linezolid solution for infusion 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 solution for infusion 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 solution for infusion was chemically incompatible when combined with ceftriaxone sodium.

Compatible Intravenous Solutions
5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP

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).

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).

4.4 Special warnings and precautions for use

Reversible myelosuppression (anemia, thrombocytopenia, leukopenia, and pancytopenia) that may be dependent on duration of therapy has been reported in some 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. Monitoring of complete blood counts should be considered for patients who are at increased risk for bleeding, who have pre-existing myelosuppression, who have severe renal insufficiency or moderate to severe hepatic impairment, who receive concomitant medications that may decrease hemoglobin levels or platelet count or function, or who receive linezolid for more than 2 weeks.

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.

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.

Lactic acidosis has been reported with the use of linezolid. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical attention.

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.

Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and opioids have been reported (see sections 4.3 and 4.5).

Where administration of linezolid 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.

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/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.

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). The clinical significance of this interaction is unknown.

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.

4.5 Interactions with other medicinal products and other forms of interaction

Linezolid is a weak, reversible, nonselective inhibitor of monoamine oxidase. Therefore, some patients receiving linezolid may experience a mild reversible enhancement on the pressor response induced by pseudoephedrine HCl or phenylpropanolamine HCl. Initial doses of adrenergic agents, such as dopamine or dopamine agonists, should be reduced and titrated to achieve the desired response.

Very rare spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic agents have been reported (see sections 4.3 and 4.4).

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).

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

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

In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis removes approximately 30% of a dose of linezolid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
Linezolid is a synthetic, antibacterial agent that belongs to a class of antimicrobials called oxazolidinones. It has *in vitro* activity against aerobic Gram-positive bacteria, some Gram-negative 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.

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

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
Susceptible organisms **Gram positive aerobes:** *Enterococcus faecalis*

Enterococcus faecium[*] *Staphylococcus aureus*[*] Coagulase negative staphylococci *Streptococcus agalactiae*[*] *Streptococcus pneumoniae*[*] *Streptococcus pyogenes*[*] Group C streptococci Group G streptococci **Gram positive anaerobes:** *Clostridium perfringens* *Peptostreptococcus anaerobius* *Peptostreptococcus* species
Resistant organisms *Haemophilus influenzae* *Moraxella catarrhalis* *Neisseria* species *Enterobacteriaceae* *Pseudomonas* species [*] Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

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 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.

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 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 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 7-8 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).

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).

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 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: The tablets contain corn starch, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and carnauba wax. The sodium (Na^+) content is 2.92 mg per 600-mg tablet (0.1 mEq per tablet, regardless of strength).

Solution for Infusion: The intravenous formulation contains sodium citrate, citric acid, and dextrose in an aqueous vehicle for intravenous administration. The sodium (Na^+) content is 0.38 mg/mL (5 mEq per 300-mL bag and 1.7 mEq per 100-mL bag).

Oral Suspension: The oral suspension contains aspartame, citric acid, colloidal silicon dioxide, flavors, mannitol, microcrystalline cellulose and carboxymethylcellulose sodium, sodium benzoate, sodium chloride, sodium citrate, sucrose, and xanthan gum. The sodium (Na+) content is 8.52 mg/5 mL (0.4 mEq/5 mL).

6.2 Incompatibilities

Solution for Infusion: Linezolid solution for infusion 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 solution for infusion was chemically incompatible when combined with ceftriaxone sodium.

6.3 Shelf life

Tablets: Refer to carton for shelf life.

Solution for Infusion: Refer to carton for shelf life.

Oral Suspension: Refer to carton for shelf life for the dry granule/powder, and 21 days for the reconstituted product.

6.4 Special precautions for storage

Tablets
Store below 30°C. Protect from light.

Solution for Infusion
Store below 30°C. It is recommended that the infusion bags be kept in the overwrap until ready to use. Protect infusion bags from freezing.

Oral suspension.
Store at 30° C. Protect from light. Keep bottles tightly closed to protect from moisture.

6.5 Nature and contents of container

Tablets
Linezolid tablet are available as follows:

600 mg (capsule shaped, white to off-white coated tablet with "ZYV" debossed on one side and "600" debossed on the other)
Blister pack of 10

Solution for Infusion
Linezolid solution for infusion is available in single-use, ready-to-use flexible plastic infusion bags in a foil laminate overwrap. The infusion bags and ports are latex-free. The infusion bags are available in the following package sizes:

300 mL bag (600 mg linezolid)

Oral Suspension
Linezolid for oral suspension is available as a dry, white to off-white, orange-flavored granule/powder. When constituted as directed, each bottle will contain 150 mL of a suspension providing the equivalent of 100 mg of linezolid per each 5 mL. Linezolid for oral suspension is supplied as follows:

100 mg/5 mL in 240-mL glass bottles

Some product strengths or pack sizes may not be available in your country.

6.6 Special precautions for disposal and other handling

Solution for Infusion Administration
Linezolid solution for infusion is supplied in single-use, ready-to-use infusion bags. Parenteral drug products should be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bag. If leaks are detected, discard the solution, as sterility may be impaired.

Linezolid solution for infusion should be administered by intravenous infusion over a period of 30 to 120 minutes. **Do not use this intravenous infusion bag in series connections**. Additives should not be introduced into this solution. If linezolid solution for infusion 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. In particular, physical incompatibilities resulted when linezolid solution for infusion was combined with the following drugs during simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isothionate, erythromycin lactobionate, phenytoin sodium, and trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when linezolid solution for infusion was combined with ceftriaxone sodium.

If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of linezolid solution for infusion with an infusion solution compatible with linezolid solution for infusion and with any other drug(s) administered via this common line.

Compatible Intravenous Solutions
5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP

Keep the infusion bags in the overwrap until ready to use. Store at room temperature. Protect from freezing. Linezolid solution for infusion may exhibit a yellow color that can intensify over time without adversely affecting potency.

Constitution of Oral Suspension
Linezolid for Oral Suspension is supplied as a powder/granule for constitution. 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. After constitution, each 5 mL of the suspension contains 100 mg of linezolid. Before using, gently mix by

inverting the bottle 3 to 5 times. Do not shake. Store constituted suspension at room temperature. Use within 21 days after constitution.

7. MANUFACTURER

Oral Suspension:
Neolpharma, Inc.,
Caguas, Puerto Rico, USA

Packager:
Pharmacia and Upjohn Company LLC,
Kalamazoo, USA

Tablet:
Viatris Pharmaceutical LLC
Road 689 Km 1.9
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