Zyvoxid, Israel 22 November 2009

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Zyvoxid

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Zyvoxid 2 mg/ml Solution for Infusion
Zyvoxid 600 mg Film Coated Tablets

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion:
Isotonic, clear, colourless to yellow, solution.

600mg Film coated tablet:
White, ovaloid, film coated tablets marked "ZYVOXID 600 mg" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Therapy is indicated only when an organism resistant to all the other antibiotics is suspected. Zyvoxid is indicated in adult and pediatric patients for the treatment of infections when known or suspected to be caused by susceptible organisms including those associated with concurrent bacteraemia such as:

- Pneumonia -community acquired and nosocomial pneumonia including multi drug resistant streptococcus pneumonia (MDRSP).
- Skin and Soft tissue infections including diabetic foot infections.
- Enterococcal infections.

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 section 4.4 and 5.1).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration

Zyvoxid solution for infusion and film coated tablets may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to either oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as linezolid has an oral biovailability of approximately 100%.

The solution for infusion should be administered over a period of 30 to 120 minutes.
The film coated tablets may be taken with or without food.

The recommended linezolid dosage should be administered IV or orally twice daily.

The recommended dosage for Zyvoxid formulations for the treatment of infections is described in Table 1.

Table 1. Dosage Guidelines for Zyvoxid

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 (see **THERAPEUTIC INDICATIONS**)

† **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 (see **PHARMACOLOGICAL PROPERTIES, Pharmacokintic Properties, Pediatric**).

‡ Oral dosing using Zyvoxid Tablets

Adult patients with infection due to MRSA should be treated with Zyvoxid 600 mg q12h.

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with Zyvoxid had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see **PHARMACOLOGICAL PROPERTIES, Pharmacokinetic Properties, Pediatric** and **Special Warnings and Special Precautions for Use, Pediatric Use**).

In controlled clinical trials, the protocol-defined duration of treatment for all infections ranged from 7 to 28 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response.

No dose adjustment is necessary when switching from intravenous to oral administration. Patients whose therapy is started with Zyvoxid I.V. Injection may be switched to Zyvoxid Tablets at the discretion of the physician, when clinically indicated.

Elderly patients: No dose adjustment is required.

Female patients: No dose adjustment is required.

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

Patients with mild to moderate renal insufficiency: (ie CL_{CR}> 30 ml/min}: No dose adjustment is required.

Patients with severe renal insufficiency CLCR < 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 haemodialysis).

Patients with impaired hepatic function: No dose adjustment is required. However, there are no pharmacokinetic data and limited clinical experience of linezolid in patients with severe hepatic insufficiency. Linezolid should be used with special caution in patients with severe hepatic insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk.

4.3 Contraindications

Hypersensitivity to linezolid or to any of the excipients in the relevant pharmaceutical form (see section 6.1).

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 Special Precautions for Use

Pseudomembranous colitis has been reported with nearly all antibacterial agents including linezolid, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent.

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.

The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. 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 receiving concomitant drugs that produce bone marrow suppression or those with a 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.

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

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

Peripheral neuropathy 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 was reported. 51 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.

Where administration of ZYVOXID 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.

In healthy volunteers, coadministration of rifampin with linezolid resulted in a 21% decrease in linezolid Cmax 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.

Pediatric Use

The safety and effectiveness of Zyvoxid for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **THERAPEUTIC INDICATIONS**):

- nosocomial pneumonia
- complicated skin and skin structure infections
- community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years)
- vancomycin-resistant Enterococcus faecium infections

The safety and effectiveness of Zyvoxid for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years.

- uncomplicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible strains only) or Streptococcus pyogenes

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.

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

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h.

Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 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 (see **PHARMACOLOGICAL PROPERTIES, Pharmacokinetic Properties, Pediatric** and **POSOLOGY AND METHOS OF ADMINISTRATION**).

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with Zyvoxid had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see **PHARMACOLOGICAL PROPERTIES, Pharmacokinetic Properties, Pediatric** and **POSOLOGY AND METHOS OF ADMINISTRATION**).

4.5 Interaction with other Medicinal Products and Other Forms of Interaction

Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not induce or inhibit the activities of clinically significant human CYP isoforms (IA2, 2C9, 2C19, 2D6, 2EI, 3A4). Therefore, no CYP450-induced drug interactions are expected with linezolid. Drugs such as warfarin and phenytoin, which aloe CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

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

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 beverage fermented soya bean products such as soy sauce). In subject receiving linezolid and tyramine doses of more than 100 mg. a significant, contpressor respondse has been observed.

Although linezolid has the potential for interaction with serotonergic agents, no. serotonin syndrome effects {eg confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) were observed in subjects receiving linezolid and dextromethorphan.

Since there is limited experience with concomitant administration of linezolid and serotonergic agents, physicians should be alert to the possibility of signs and symptoms of serotonin syndrome (e.g., hyperpyrexia, and cognitive dysfunction) in patients receiving such concomitant therapy.

Very rare spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic agents have been reported.

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 Cmax 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 Pregnancy and Lactation

There are no adequate data from the use of linezolid in pregnant women. Studies in animals have shown reproductive effects (see section 5.3). The potential risk for humans is unknown.
Zyvoxid should not be used during pregnancy unless clearly necessary i.e. only if the potential benefit outweighs the potential risk.

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

4.7 Effects on Ability to Drive and Use Machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable Effects

Clinical Trials: Adverse events considered drug-related in controlled clinical trials with an incidence of at least 1% were:

Gastrointestinal Disorders: Abdominal pain/cramps/distension, diarrhea, nausea, vomiting.

Infections and Infestations: Moniliasis.

Investigations: Abnormal hematology tests, abnormal liver function tests.

Nervous System Disorders: Headache, taste alteration.

Post marketing:

Blood and Lymphatic System Disorders: Reversible anemia, leucopenia, thrombocytopenia, pancytopenia.

Eye Disorders: Optic neuropathy 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 durations of 28 days (see section 4.4 Special Warnings and Special Precautions for Use).

Immune System Disorders: Anaphylaxis.

Metabolism and Nutrition Disorders: Lactic acidosis. (see section 4.4 Special Warnings and Special Precautions for Use).

Nervous System Disorders: Peripheral neuropathy, convulsions (see section 4.4 Special Warnings and Special Precautions for Use).

Skin and Subcutaneous Tissue Disorders: Rash, angioedema. Very rare reports of bullous skin disorders such as those described as Stevens Johnson syndrome have been received.

Gastrointestinal Disorders: Tongue discoloration. Superficial tooth discoloration has been reported very rarely with the use of linezolid. The discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome.

Pediatric Patients

The safety of Zyvoxid formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with Zyvoxid were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid: vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. Table 2 shows the incidence of adverse events reported in at least 2% of pediatric patients treated with Zyvoxid in these trials.

Table 2. Incidence (%) of Adverse Events Reported in ≥2% of Pediatric Patients Treated with Zyvoxid in Comparator-Controlled Clinical Trials

Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
	Zyvoxid (n=248)	Cefadroxil (n = 251)	Zyvoxid (n = 215)	Vancomycin (n=101)
Fever	2.9	3.6	14.1	14.1
Diarrhea	7.8	8.0	10.8	12.1
Vomiting	2.9	6.4	9.4	9.1
Sepsis	0	0	8.0	7.1
Rash	1.6	1.2	7.0	15.2
Headache	6.5	4.0	0.9	0
Anemia	0	0	5.6	7.1
Thrombocytopenia	0	0	4.7	2.0
Upper respiratory infection	3.7	5.2	4.2	1.0
Nausea	3.7	3.2	1.9	0
Dyspnea	0	0	3.3	1.0
Reaction at site of injection or of vascular catheter	0	0	3.3	5.1
Trauma	3.3	4.8	2.8	2.0
Pharyngitis	2.9	1.6	0.5	1.0
Convulsion	0	0	2.8	2.0
Hypokalemia	0	0	2.8	3.0
Pneumonia	0	0	2.8	2.0
Thrombocythemia	0	0	2.8	2.0
Cough	2.4	4.0	0.9	0
Generalized abdominal pain	2.4	2.8	0.9	2.0
Localized abdominal pain	2.4	2.8	0.5	1.0
Apnea	0	0	2.3	2.0
Gastrointestinal bleeding	0	0	2.3	1.0
Generalized edema	0	0	2.3	1.0
Loose stools	1.6	0.8	2.3	3.0
Localized pain	2.0	1.6	0.9	0

Skin disorder	2.0	0	0.9	1.0

* Patients 5 through 11 years of age received Zyvoxid 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received Zyvoxid 600 mg PO q12h or cefadroxil 500 mg PO q12h.
† Patients from birth through 11 years of age received Zyvoxid 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Table 3 shows the incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

Table 3. Incidence (%) of Drug-related Adverse Events Occurring in >1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-Controlled Clinical Trials

Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
	Zyvoxid (n=248)	Cefadroxil (n=251)	Zyvoxid (n=215)	Vancomycin (n=101)
% of patients with ≥1 drug-related adverse event	19.2	14.1	18.8	34.3
% of patients discontinuing due to a drug-related adverse event	1.6	2.4	0.9	6.1
Diarrhea	5.7	5.2	3.8	6.1
Nausea	3.3	2.0	1.4	0
Headache	2.4	0.8	0	0
Loose stools	1.2	0.8	1.9	0
Thrombocytopenia	0	0	1.9	0
Vomiting	1.2	2.4	1.9	1.0
Generalized abdominal pain	1.6	1.2	0	0
Localized abdominal pain	1.6	1.2	0	0
Anemia	0	0	1.4	1.0
Eosinophilia	0.4	0.4	1.4	0
Rash	0.4	1.2	1.4	7.1
Vertigo	1.2	0.4	0	0
Oral moniliasis	0	0	0.9	4.0
Fever	0	0	0.5	3.0
Pruritus at non-application site	0.4	0	0	2.0
Anaphylaxis	0	0	0	10.1‡

* Patients 5 through 11 years of age received Zyvoxid 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received Zyvoxid 600 mg PO q12h or cefadroxil 500 mg PO q12h.
† Patients from birth through 11 years of age received Zyvoxid 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.
‡ These reports were of 'red-man syndrome', which were coded as anaphylaxis.

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 haemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion. The primary metabolites of linezolid are also removed 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

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, 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.

Susceptibility
Only micro-organisms relevant to the given clinical indications are presented here.

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.

Plasma linezolid Cmax and Cmin (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 metabolizsed 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 sections 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 metabolized by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism (see sections 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 600mg 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.

Pediatric: The pharmacokinetics of linezolid following a single IV dose were investigated in pediatric patients ranging in age from birth through 17 years (including premature and full-term neonates), in healthy adolescent subjects ranging in age from 12 through 17 years, and in pediatric patients ranging in age from 1

week through 12 years. The pharmacokinetic parameters of linezolid are summarized in Table 4 for the pediatric populations studied and healthy adult subjects after administration of single IV doses.

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

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours (q12h). Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h (see **POSOLOGY AND METHOS OF ADMINISTRATION**).

Table 4. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

Age Group	C_{max} µg/mL	V_{ss} L/kg	AUC* µg•h/mL	$t_{1/2}$ hrs	CL mL/min/kg
Neonatal Patients Pre-term** < 1 week (N=9)†	12.7 (30%) [9.6, 22.2]	0.81 (24%) [0.43, 1.05]	108 (47%) [41, 191]	5.6 (46%) [2.4, 9.8]	2.0 (52%) [0.9, 4.0]
Full-term*** < 1 week (N=10)†	11.5 (24%) [8.0, 18.3]	0.78 (20%) [0.45, 0.96]	55 (47%) [19, 103]	3.0 (55%) [1.3, 6.1]	3.8 (55%) [1.5, 8.8]
Full-term*** ≥ 1 week to ≤ 28 days (N=10)†	12.9 (28%) [7.7, 21.6]	0.66 (29%) [0.35, 1.06]	34 (21%) [23, 50]	1.5 (17%) [1.2, 1.9]	5.1 (22%) [3.3, 7.2]
Infant Patients > 28 days to < 3 Months (N=12)†	11.0 (27%) [7.2, 18.0]	0.79 (26%) [0.42, 1.08]	33 (26%) [17, 48]	1.8 (28%) [1.2, 2.8]	5.4 (32%) [3.5, 9.9]
Pediatric Patients 3 months through 11 years† (N=59)	15.1 (30%) [6.8, 36.7]	0.69 (28%) [0.31, 1.50]	58 (54%) [19, 153]	2.9 (53%) [0.9, 8.0]	3.8 (53%) [1.0, 8.5]
Adolescent Subjects and Patients 12 through 17 years‡ (N=36)	16.7 (24%) [9.9, 28.9]	0.61 (15%) [0.44, 0.79]	95 (44%) [32, 178]	4.1 (46%) [1.3, 8.1]	2.1 (53%) [0.9, 5.2]
Adult Subjects§ (N= 29)	12.5 (21%) [8.2, 19.3]	0.65 (16%) [0.45, 0.84]	91 (33%) [53, 155]	4.9 (35%) [1.8, 8.3]	1.7 (34%) [0.9, 3.3]

* AUC = Single dose $AUC_{0-\infty}$
** In this data set, "pre-term" is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days)
*** In this data set, "full-term" is defined as ≥34 weeks gestational age
† Dose of 10 mg/kg
‡ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg
§ Dose normalized to 600 mg
C_{max} = Maximum plasma concentration;
V_{ss}= Volume of distribution;
AUC = Area under concentration-time curve;
$t_{1/2}$ = Apparent elimination half-life;
CL = Systemic clearance normalized for body weight

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/lg/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 (0.5 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 myelosupression 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 in males dosed 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.

Similar changes were not observed in female rats. Sensitive morpohologic 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 compatible 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

Solution for infusion: Dextrose monohydrate (glucose)
Sodium citrate dihydrate
Citric acid anhydrous
Hydrochloric acid sodium hydroxide
Water for injections

Film coated tablets: Tablet core:
Microcrystalline cellulose
Corn starch
Sodium starch glycollate
Hydroxypropyl cellulose
Magnesium stearate

Film coat:
Hydroxypropylmethylcellulose (E464)
Titanium dioxide (E171)
Polyethylene glycol

Carnauba wax (E903)
Red ink

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

Zyvoxid 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.

Film coated tablets: Not appropriate

6.3 Special Precautions for Storage

Solution for injection: store below 25°
Solution for infusion: Keep bags in foil overwrap and carton until ready to use.
Tablets: store in a cool and dark place

6.4 Nature and Contents of Container

Solution for infusion: Single use, ready-to-use, Excel® film infusion bags sealed inside a foil laminate overwrap. Bags contain either 100 ml, 200 ml or 300 ml solution and are packaged in a box.

Film coated tablets: Polyviny1chloride {PVC)/foil blisters of 10 tablets packaged in a box. Each box contains 10 tablets.

6.5 Instructions for Use and Handling

Solution for infusion: 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.

Film coated tablets: No special requirements.

Manufacturer: Zyvoxid I.V: Pharmacia Norway AS
Zyvoxid tables: Pfizer Pharmaceuticals LLC, Puerto Rico.

For: Pfizer Pharmaceuticals Israel Ltd.9 Shenkar st., Herzelyia 46725