SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zyvoxid® I.V. 2 mg/ml Solution for Infusion
Zyvoxid® 600 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for infusion:
1 ml contains 2 mg linezolid.
Excipients with known effect: each 1 ml also contains 45.7 mg glucose and 0.38 mg sodium.
600 mg tablet:
Each tablet contains 600 mg linezolid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion:
Isotonic, clear, colourless to yellow solution with pH range of 4.4-5.2.

600mg tablet:
A white to off-white coated tablet with "ZYV" debossed on one side and "600" debossed on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapy is indicated only when an organism resistant to all 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:
1) Pneumonia - community acquired and nosocomial pneumonia including multi drug resistant streptococcus pneumonia (MDRSP).
2) Skin and soft tissue infections including diabetic foot infections.
3) 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).

Linezolid should only be initiated after consultation with a relevant specialist such as a microbiologist or infectious diseases specialist.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Zyvoxid® solution for infusion and 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 tablets may be taken with or without food.

The recommended linezolid dosage should be administered I.V. 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 I.V. or oral‡ q8h	600 mg I.V. or oral‡ q12h	10 to 14
Community-acquired pneumonia, including concurrent bacteraemia			
Nosocomial pneumonia			
Vancomycin-resistant Enterococcus faecium infections, including concurrent bacteraemia	10 mg/kg I.V. or oral‡ q8h	600 mg I.V. 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, Pharmacokinetic properties, Pediatric population).

‡ 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 Grampositive 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 population and CLINICAL PARTICULARS, Special warnings and 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: (i.e., CL_{CR}> 30 ml/min): No dose adjustment is required.

Patients with severe renal insufficiency 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 haemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by haemodialysis, 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 listed in section 6.1.

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

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

- Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.

- Patients taking any of the following medications: serotonin re-uptake inhibitors (see section 4.4), tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine), pethidine or buspirone.

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

4.4 Special warnings and precautions for use

Myelosuppression
Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pretreatment levels. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with linezolid may be at greater risk of experiencing blood dyscrasias than younger patients. Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis. Therefore, close monitoring of blood counts is recommended in patients who: have pre-existing anaemia, granulocytopenia or thrombocytopenia; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; receive more than 10-14 days of therapy. Linezolid should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible.

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

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

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

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

Mortality imbalance in a clinical trial in patients with catheter-related Gram positive bloodstream infections
Excess mortality was seen in patients treated with linezolid, relative to vancomycin/dicloxacillin/oxacillin, in an open-label study in seriously ill patients with intravascular catheter-related infections [78/363 (21.5%) vs 58/363 (16.0%)]. The main factor influencing the mortality rate was the Gram positive infection status at baseline. Mortality rates were similar in patients with infections caused purely by Gram positive organisms (odds ratio 0.96; 95% confidence interval: 0.58-1.59) but were significantly higher (p=0.0162) in the linezolid arm in patients with any other pathogen or no pathogen at baseline (odds ratio 2.48; 95% confidence interval: 1.38-4.46). The greatest imbalance occurred during treatment

and within 7 days following discontinuation of study drug. More patients in the linezolid arm acquired Gram negative pathogens during the study and died from infection caused by Gram negative pathogens and polymicrobial infections. Therefore, in complicated skin and soft tissue infections linezolid should only be used in patients with known or possible co-infection with Gram negative organisms if there are no alternative treatment options available (see section 4.1). In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

Antibiotic-associated diarrhoea and colitis

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

Lactic acidosis
Lactic acidosis has been reported with the use of linezolid. Patients who develop signs and symptoms of metabolic acidosis including recurrent nausea or vomiting, abdominal pain, a low bicarbonate level, or hyperventilation while receiving linezolidshould receive immediate medical attention. If lactic acidosis occurs, the benefits of continued use of linezolid should be weighed against the potential risks.

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

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

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

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

If peripheral or optic neuropathy occurs, the continued use of Linezolid should be weighed against the potential risks.

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

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

Monoamine oxidase inhibitors
Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI); however, at the doses used for antibacterial therapy, it does not exert an anti-depressive effect. There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (see sections 4.3 and 4.5).

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

Superinfection
The effects of linezolid therapy on normal flora have not been evaluated in clinical trials.

The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. For example, approximately 3% of patients receiving the recommended linezolid doses experienced drug-related candidiasis during clinical trials. Should superinfection occur during therapy, appropriate measures should be taken.

Special populations
Linezolid should be used with special caution in patients with severe renal insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk (see sections 4.2 and 5.2).

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk (see sections 4.2 and 5.2).

Impairment of fertility
Linezolid reversibly decreased fertility and induced abnormal sperm morphology in adult male rats at exposure levels approximately equal to those expected in humans; possible effects of linezolid on the human male reproductive system are not known (see section 5.3).

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

Controlled clinical trials did not include patients with diabetic foot lesions, decubitus or ischaemic lesions, severe burns or gangrene. Therefore, experience in the use of linezolid in the treatment of these conditions is limited.

Excipients
Each ml of the solution contains 45.7 mg (i.e., 13.7 g/300 ml) glucose. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance. Each ml of solution also contains 0.38 mg (114 mg/300 ml) sodium. The sodium content should be taken into account in patients on a controlled sodium diet.

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 Grampositive 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 pharmacokinetics of linezolid have been evaluated in pediatric patients from birth to 17 years of age. In general, weight-based clearance of linezolid gradually decreases with increasing age of pediatric patients. However, in preterm (gestational age < 34 weeks) neonates < 7 days of age, linezolid clearance is often lower than in full-term neonates < 7 days of age. Consequently, preterm neonates < 7 days of age may need an alternative linezolid dosing regimen of 10 mg/kg every 12 hours .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 population and Posology and method 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 population and Posology and method of administration).

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI). There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients on concomitant medications that might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (see sections 4.3 and 4.4).

Potential interactions producing elevation of blood pressure

In normotensive healthy volunteers, linezolid enhanced the increases in blood pressure caused by pseudoephedrine and phenylpropanolamine hydrochloride. Co-administration of linezolid with either pseudoephedrine or phenylpropanolamine resulted in mean increases in systolic blood pressure of the order of 30-40 mmHg, compared with 11-15 mmHg increases with linezolid alone, 14-18 mmHg with either pseudoephedrine or phenylpropanolamine alone and 8-11 mmHg with placebo. Similar studies in hypertensive subjects have not been conducted. It is recommended that doses of drugs with a vasopressive action, including dopaminergic agents, should be carefully titrated to achieve the desired response when co-administered withlinezolid.

Potential serotonergic interactions

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 and hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

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

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

Use with tyramine-rich foods

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

Drugs metabolised by cytochrome P450

Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450-induced drug interactions are expected with linezolid.

Rifampicin

The effect of rifampicin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased the linezolid C_{max} and AUC by a mean 21% [90% CI, 15, 27] and a mean 32% [90% CI, 27, 37], respectively. The mechanism of this interaction and its clinical significance are unknown.

Warfarin

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

4.6 Fertility, pregnancy and lactation

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 2,000 adult patients who received the recommended linezolid doses for up to 28 days.

Those most commonly reported were diarrhoea (8.4%), headache (6.5%), nausea (6.3%) and vomiting (4.0%).

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

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

The following undesirable effects have been observed and reported during treatment with linezolid with the following frequencies: 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); Not known (cannot be estimated from the available data)

System Organ Class	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 available data)
Infections and infestations	candidiasis, oral candidiasis, vaginal candidiasis, fungal infections	vaginitis	antibiotic-associated colitis, including pseudomembranous colitis*		
Blood and the	anaemia*†	leucopenia*,	pancytopenia*		myelosuppression

System Organ Class	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 available data)
lymphatic system disorders		neutropenia, thrombocytopenia*, eosinophilia			*, sideroblastic anaemia*
Immune system disorders					anaphylaxis
Metabolism and nutrition disorders		hyponatraemia			lactic acidosis*
Psychiatric disorders	insomnia				
Nervous system disorders	headache, taste perversion (metallic taste), dizziness	convulsions*, hypoaesthesia, paraesthesia			serotonin syndrome**, peripheral neuropathy*
Eye disorders		blurred vision*	changes in visual field defect*		optic neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*
Ear and labyrinth disorders		tinnitus			
Cardiac disorders		arrhythmia (tachycardia)			
Vascular disorders	hypertension	transient ischaemic attacks, phlebitis, thrombophlebitis			
Gastrointestinal disorders	diarrhoea, nausea, vomiting, localised or general abdominal pain, constipation, dyspepsia	pancreatitis, gastritis, abdominal distention, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder	superficial tooth discolouration		
Hepato-biliary disorders	abnormal liver function test, increased AST, ALT or alkaline phosphatase	increased total bilirubin			
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria, dermatitis, diaphoresis			bullous disorders such as those described as Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, alopecia

System Organ Class	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 available data)
Renal and urinary disorders	increased BUN	renal failure, increased creatinine, polyuria			
Reproductive system and breast disorders		vulvovaginal disorder			
General disorders and administration site conditions	fever, localised pain	chills, fatigue, injection site pain, increased thirst			
Investigations	Chemistry Increased LDH, creatine kinase, lipase, amylase or non fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate. Haematology Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.	Chemistry Increased sodium or calcium. Decreased non fasting glucose. Increased or decreased chloride. Haematology Increased reticulocyte count. Decreased neutrophils.			

* See section 4.4.
** See sections 4.3 and 4.5
† See below

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

†In controlled clinical trials where linezolid was administered for up to 28 days, 2.0% of the patients reported anaemia. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia

when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for >28 days. The proportion of cases reporting drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for >28 days.

Paediatric population

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 the study of hospitalized pediatric patients (birth through 11 years) with Grampositive 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.

Of the pediatric patients treated for uSSSIs, 19.2% of ZYVOXID® -treated and 14.1% of comparator-treated patients experienced at least one drug-related adverse event. For all other indications, 18.8% of ZYVOXID® -treated and 34.3% of comparator-treated patients experienced at least one drug-related adverse event.

Table 2 shows the incidence of all-causality, treatment-emergent adverse reactions 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 2. Incidence (%) of Treatment-Emergent Adverse Reactions Occurring in > 1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-Controlled Clinical Trials

ADVERSE REACTIONS	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
	ZYVOXID® (n=248)	Cefadroxil (n=251)	ZYVOXID® (n=215)	Vancomycin (n=101)
Diarrhoea	7.8	8.0	10.8	12.1
Vomiting	2.9	6.4	9.4	9.1
Headache	6.5	4.0	0.9	0
Anaemia	0	0	5.6	7.1
Thrombocytopenia	0	0	4.7	2.0
Nausea	3.7	3.2	1.9	0
Generalized abdominal pain	2.4	2.8	0.9	2.0
Localized abdominal pain	2.4	2.8	0.5	1.0
Loose stools	1.6	0.8	2.3	3.0
Eosinophilia	0.4	0.8	1.9	1.0
Pruritus at non-application site	0.8	0.4	1.4	2.0
Vertigo	1.2	0.4	0	0

***** Patients 5 through 11 years of age received ZYVOXID® 10 mg/kg by mouth every 12 hours or cefadroxil 15 mg/kg by mouth every 12 hours. Patients 12 years or older received ZYVOXID® 600 mg by mouth every 12 hours or cefadroxil 500 mg by mouth every 12 hours.

† Patients from birth through 11 years of age received ZYVOXID®10 mg/kg intravenously by mouth every 8 hours or vancomycin 10 to 15 mg/kg intravenously every 6-24 hours, depending on age and renal clearance.

Of the pediatric patients treated for uSSSIs, 1.6% of ZYVOXID®-treated and 2.4% of comparator-treated patients discontinued treatment due to drug-related adverse events. For all other indications, discontinuations due to drug-related adverse events occurred in 0.9% of ZYVOXID®-treated and 6.1% of comparator-treated patients.

ZYVOXID® has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOXID® and

13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOXID® and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOXID® appears to be dependent on duration of therapy (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOXID®; the role of linezolid in these events cannot be determined [see section 4.4]. The incidence of pediatric patients with at least one substantially abnormal haematologic or serum chemistry value is presented in Table 3.

Table 3. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOXID®

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections†		All Other Indications‡	
	ZYVOXID®	Cefadroxil	ZYVOXID®	Vancomycin
Hemoglobin (g/dL)	0.0	0.0	15.7	12.4
Platelet count (x 10^3/mm^3)	0.0	0.4	12.9	13.4
WBC (x 10^3/mm^3)	0.8	0.8	12.4	10.3
Neutrophils (x 10^3/mm^3)	1.2	0.8	5.9	4.3

* <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline;
<75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

† Patients 5 through 11 years of age received ZYVOXID® 10 mg/kg by mouth every 12 hours or cefadroxil 15 mg/kg by mouth every 12 hours. Patients 12 years or older received ZYVOXID® 600 mg by mouth every 12 hours or cefadroxil 500 mg by mouth every 12 hours.

‡ Patients from birth through 11 years of age received ZYVOXID® 10 mg/kg intravenously by mouth every 8 hours or vancomycin 10 to 15 mg/kg intravenously every 6-24 hours, depending on age and renal clearance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose

No specific antidote is known.

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antibacterials,ATC code: J 01 X X 08

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

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

Breakpoints
Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and enterococci are Susceptible ≤ 4mg/L and Resistant >4 mg/L. For streptococci (including *S. pneumoniae*) the breakpoints are Susceptible ≤ 2 mg/L and Resistant >4 mg/L.
Non-species related MIC breakpoints are Susceptible ≤ 2 mg/L and Resistant > 4 mg/L. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that have not been given a specific breakpoint and not for those species where susceptibility testing is not recommended.

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

Category
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

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

Resistance

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

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

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

Information from clinical trials

Studies in the paediatric population:
In an open study, the efficacy of linezolid (10 mg/kg q8h) was compared to vancomycin (10-15mg/kg q6- 24h) in treating infections due to suspected or proven resistant grampositive pathogens(including nosocomial pneumonia, complicated skin and skin structure infections, catheter related bacteraemia, bacteraemia of unknown source, and other infections), in

children from birth to 11 years. Clinical cure rates in the clinically evaluable population were 89.3% (134/150) and 84.5%(60/71) for linezolid and vancomycin, respectively (95%CI: -4.9, 14.6).

5.2 Pharmacokinetic properties

Zyvoxid® 600mg & Zyvoxid® I.V. 2 mg/ml primarily contain (s)-linezolid which is biologically active and is metabolised to form inactive derivatives.

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

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, Cmax and Cmin 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 Cmax, respectively. In a small study of subjects with ventricular-peritoneal shunts and essentially non-inflamed meninges, the ratio of linezolid in cerebrospinal fluid to plasma at Cmax was 0.7:1.0 after multiple linezolid dosing.

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.

Biotransformation
Linezolid is primarily metabolised by oxidation of the morpholine ring resulting mainly in the formation of two inactive open-ring carboxylic acid derivatives; the aminoethoxyacetic acid metabolite (PNU-142300) and the hydroxyethyl glycine metabolite (PNU-142586). The hydroxyethyl glycine metabolite (PNU-142586) is the predominant human metabolite and is believed to be formed by a non-enzymatic process. The aminoethoxyacetic acid metabolite (PNU-142300) is less abundant. Other minor, inactive metabolites have been characterised.

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

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

Special populations

Renal impairment: After single doses of 600 mg, there was a 7-8 fold increase in exposure to the two primary metabolites of linezolid in the plasma of patients with severe renal insufficiency (i.e., creatinine clearance < 30 ml/min). However, there was no increase in AUC of parent drug. Although there is some removal of the major metabolites of linezolid by haemodialysis, metabolite plasma levels after single 600 mg doses were still considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

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

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

Hepatic impairment: Limited data indicate that the pharmacokinetics of linezolid, PNU-142300 and PNU-142586 are not altered in patients with mild to moderate hepatic insufficiency (i.e., Child-Pugh class A or B). The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (i.e., Child-Pugh class C) have not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism (see sections 4.2 and 4.4).

Paediatric population (< 18 years old):
The pharmacokinetics of linezolid following a single intravenous 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 intravenous doses.
The Cmax and the volume of distribution (Vss) of linezolid are similar regardless of age in pediatric patients. However, plasma clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, weight-based 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 a shorter half life as compared with adults. As the age of pediatric patients increases, the weight-based clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population. There is increased 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 relative to adolescents or adults dosed every 12 hours. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg every 8 hours. Pediatric patients 12 years and older should receive 600 mg every 12 hours [see CLINICAL PARTICULARS, Posology and method 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} mcg/ml	V_{ss} L/kg	AUC* mcg•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 halflife; CL = Systemic clearance normalized for body weight

Table 5. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOXID®

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections†		All Other Indications‡	
	ZYVOXID®	Cefadroxil	ZYVOXID®	Vancomycin
ALT (U/L)	0.0	0.0	10.1	12.5
Lipase (U/L)	0.4	1.2	---	---
Amylase (U/L)	---	---	0.6	1.3
Total bilirubin (mg/dL)	---	---	6.3	5.2
Creatinine (mg/dL)	0.4	0.0	2.4	1.0

* >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

† Patients 5 through 11 years of age received ZYVOXID® 10 mg/kg by mouth every 12 hours or cefadroxil 15 mg/kg by mouth every 12 hours. Patients 12 years or older received ZYVOXID® 600 mg by mouth every 12 hours or cefadroxil 500 mg by mouth every 12 hours.

‡ Patients from birth through 11 years of age received ZYVOXID® 10 mg/kg intravenously/by mouth every 8 hours or vancomycin 10 to 15 mg/kg intravenously every 6-24 hours, depending on age and renal clearance.

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

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

5.3 Preclinical safety data

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those in humans. In sexually mature animals these effects were reversible. However, these effects did not reverse in juvenile animals treated with linezolid for nearly the entire period of sexual maturation. Abnormal sperm morphology in testis of adult male rats, and epithelial cell hypertrophy and hyperplasia in the epididymis were noted. Linezolid appeared to affect the maturation of rat spermatozoa. Supplementation of testosterone had no effect on linezolid-mediated fertility effects. Epididymal hypertrophy was not observed in dogs treated for 1 month, although changes in the weights of prostate, testes and epididymis were apparent.

In sexually mature male rats exposed to drug as juveniles, mildly decreased fertility was observed following treatment with linezolid through most of their period of sexual development (50 mg/kg/day from days 7 to 36 of age, and 100 mg/kg/day from days 37 to 55 of age), with exposures up to 1.7 times greater than mean AUCs observed in pediatric patients aged 3 months to 11 years. Decreased fertility was not observed with shorter treatment periods, corresponding to exposure *in utero* through the early neonatal period (gestation day 6 through postnatal day 5), neonatal exposure (postnatal days 5 to 21), or to juvenile exposure (postnatal days 22 to 35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats treated from postnatal day 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 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 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. In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) at low exposure levels 0.06 times compared to the expected human exposure based on AUCs. The species is known to be sensitive to the effects of 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 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 of 3 male rats after 6 months of dosing, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The optic nerve degeneration observed was microscopically comparable to spontaneous unilateral optic nerve degeneration reported in aging rats and may be an exacerbation of common background change.

Preclinical data, based on conventional studies of repeated-dose toxicity and genotoxicity, revealed no special hazard for humans beyond those addressed in other sections of this Summary of Product Characteristics. Carcinogenicity/oncogenicity studies have not been conducted in view of the short duration of dosing and lack of genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solution for infusion:
Glucose monohydrate
Sodium citrate dihydrate
Citric acid anhydrous
Hydrochloric acid
Sodium hydroxide
Water for injections

600mg tablet:
Microcrystalline cellulose
Corn starch
Sodium starch glycollate
Hydroxypropyl cellulose
Magnesium stearate
Opadry white YS-1-18202-A
Carnauba wax

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).

Linezolid 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.

600mg tablets: Not applicable.

6.3 Shelf life

Solution for infusion:
Before opening: The expiry date of the product is indicated on the packaging materials.

After opening: From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.
600mg tablets:
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Solution for infusion:
Store below 25°C.
Store in the original package (overwrap and carton) until ready to use.
For storage conditions after first opening of the medicinal product, see section 6.3.
600mg tablets:
Store below 25°C, protect from light.

6.5 Nature and contents of container

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

600mg tablets: Polyvinyl chloride {PVC)/foil blisters of either 10,30 or 100 tablets, packaged in a box.

Not all package sizes may be marketed.

6.6 Special precautions for disposal and other handling

Solution for infusion:
For single use only. 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. The solution should be visually inspected prior to use and only clear solutions, without particles should be used. Do not use these bags in series connections. Any unused solution must be discarded. No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not reconnect partially used bags.

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

600 mg tablets:
No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Solution for infusion:
Fresenius Kabi Norge AS, Halden, Norway

600 mg tablets:
PFIZER INC, New York 10017, USA

8. License HOLDER:

Pfizer PFE Pharmaceuticals Israel Ltd.9 Shenkar st., Herzelyia 46725

9. License number:

Solution for infusion:

125-81-30502

600 mg tablets:

122-61-30245-01

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