Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Linezolid 600 mg tablets.

2. Qualitative and quantitative composition

Each tablet contains 600 mg linezolid.

Excipient(s) with known effect:

Each Linezolid film-coated tablet contains 200 mg of lactose monohydrate.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Tablets

Visual appearance: White to off-white coloured, oval shaped, bevelled edges, biconvex, film

coated tablets, having scoreline on one side and plain on other side.

'The tablets can be divided into two equal halves'

4. Clinical particulars

4.1 Therapeutic indications

Linezolid is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Linezolid is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a

concomitant Gram-negative pathogen is documented or suspected [see Warnings and Precautions (4.4)

Nosocomial pneumonia

Community acquired pneumonia

Linezolid is indicated in adults for the treatment of community acquired pneumonia and nosocomial pneumonia when known or suspected to be caused by susceptible Gram-positive bacteria. In determining whether Linezolid is an appropriate treatment, the results of microbiological tests or information on the prevalence of resistance to antibacterial agents among Gram positive bacteria should be taken into consideration. (See section 5.1 for the appropriate organisms).

Linezolid is not active against infections caused by Gram negative pathogens. Specific therapy against Gram negative organisms must be initiated concomitantly if a Gram-negative pathogen is documented or suspected.

Complicated skin and soft tissue infections.

Linezolid is indicated in adults for the treatment of complicated skin and soft tissue infections only when microbiological testing has established that the infection is known to be caused by susceptible Gram-positive bacteria.

Linezolid is not active against infections caused by Gram negative pathogens. Linezolid should only be used in patients with complicated skin and soft tissue infections with known or possible co-infection with Gram negative organisms if there are no alternative treatment options available. In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

Linezolid should only be initiated in a hospital environment and after consultation with a relevant specialist such as a microbiologist or infectious diseases specialist

Vancomycin-resistant Enterococcus faecium Infections

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

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

4.2 Posology and method of administration

To reduce the development of drug-resistant bacteria and maintain the effectiveness of linezolid and other antibacterial drugs, linezolid should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy

Linezolid solution for infusion, film-coated tablets or oral suspension 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 bioavailability of approximately 100%.

Recommended dosage and duration of treatment for adults: The duration of treatment is dependent on the pathogen, the site of infection and its severity, and on the patient's clinical response.

The following recommendations for duration of therapy reflect those used in the clinical trials. Shorter treatment regimens may be suitable for some types of infection but have not been evaluated in clinical trials.

The maximum treatment duration is 28 days. The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established (see section 4.4).

No increase in the recommended dosage or duration of treatment is required for infections associated with concurrent bacteraemia.

Table 1. Dosage Guidelines for Linezolid

<table>
<tr><th rowspan="2">Infection*</th><th>Dosage and Route of Administration</th><th rowspan="2">Recommended Duration of Treatment (consecutive days)</th></tr>
<tr><th>Adults and Adolescents (12 Years and Older)</th></tr>
<tr><td>Nosocomial pneumonia</td><td rowspan="3">600 mg oral every 12 hours</td><td rowspan="3">10 to 14</td></tr>
<tr><td>Community-acquired pneumonia, including concurrent bacteremia</td></tr>
<tr><td>Complicated skin and skin structure infections</td></tr>
<tr><td>Vancomycin-resistant Enterococcus faecium infections, including concurrent bacteremia</td><td>600 mg oral every 12 hours</td><td>14 to 28</td></tr>
<tr><td>Uncomplicated skin and skin structure infections</td><td>Adolescents: 600 mg oral every 12 hours</td><td>10 to 14</td></tr>
</table>

Method of administration

The recommended linezolid dosage should be administered orally twice daily.

Route of administration: Oral use.

The tablets may be taken with or without food.

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-HT1 receptor agonists (triptans), directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, 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, leukopenia, 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, and in patients with moderate to severe hepatic impairment. 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 or moderate to severe hepatic impairment; 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 linezolid should receive immediate medical attention. If lactic acidosis occurs, the benefits of continued use of linezolid should be weighed against the potential risks.

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), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine) [see Interaction with other medicinal products and other forms of interaction (4.5) and Pharmacological properties (5)].

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) and opioids have been reported (see section 4.5). 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.

Rhabdomyolysis

Rhabdomyolysis has been reported with the use of linezolid. Linezolid should be used with caution in patients with pre-disposing factors for rhabdomyolysis. If signs or symptoms of rhabdomyolysis are observed, linezolid should be discontinued and appropriate therapy initiated.

Hyponatraemia and SIADH

Hyponatraemia and/or Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) have been observed in some patients treated with linezolid. It is recommended that serum sodium levels are monitored regularly in patients at risk of hyponatraemia such as elderly patients or patients taking medicines that may lower blood sodium levels (e.g. thiazide diuretics such as hydrochlorothiazide).

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.

Hypoglycaemia

Post marketing cases of symptomatic hypoglycaemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycaemic agents when treated with linezolid, a reversible, nonselective MAO inhibitor. Some MAO inhibitors have been associated with hypoglycaemic episodes in diabetic patients receiving insulin or hypoglycaemic agents. While a causal relationship between linezolid and hypoglycaemia has not been established, diabetic patients should be cautioned of potential hypoglycaemic reactions when treated with linezolid.

If hypoglycaemia occurs, a decrease in the dose of insulin or oral hypoglycaemic agent, or discontinuation of oral hypoglycaemic agent, insulin, or linezolid may be required.

Development of Drug-Resistant Bacteria

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

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.

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk

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); 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).

Adrenergic and Serotonergic Agents

Linezolid has the potential for interaction with adrenergic and serotonergic agents.

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) and opioids, 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 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.

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 Pregnancy and Lactation

Pregnancy

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

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults:

The safety of linezolid formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days.

Of the patients treated for uncomplicated skin and skin structure infections (uSSSIs), 25.4% of linezolid treated and 19.6% of comparator-treated patients experienced at least one drug-related adverse event. For all other indications, 20.4% of linezolid-treated and 14.3% 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 at least 1% of adult patients in these trials by dose of linezolid.

Table 2. Incidence (%) of Treatment–Emergent Adverse Reactions Occurring in >1% of Adult	**Uncomplicated Skin and Skin Structure Infections#**	**All Other Indications**

Patients Treated with linezolid in Comparator-Controlled Clinical Trials ADVERSE REACTIONS			
Linezolid 400 mg by mouth every 12 hours (n=548)	**Clarithromycin 250 mg by mouth every 12 hours (n=537)**	**Linezolid 600 mg every 12 hours (n=1498)**	**All Other Comparators* (n=1464)**
Headache	8.8	8.4	5.7	4.4
Diarrhea	8.2	6.1	8.3	6.4
Nausea	5.1	4.5	6.6	4.6
Vomiting	2.0	1.5	4.3	2.3
Dizziness	2.6	3.0	1.8	1.5
Rash	1.1	1.1	2.3	2.6
Anaemia	0.4	0	2.1	1.4
Taste alteration	1.8	2.0	1.0	0.3
Vaginal moniliasis	1.8	1.3	1.1	0.5
Oral moniliasis	0.5	0	1.7	1.0

Abnormal liver function tests	0.4	0.2	1.6	0.8
Fungal infection	1.5	0.2	0.3	0.2
Tongue discoloration	1.3	0	0.	3 0
Localized abdominal pain	1.3	0.6	1.2	0.8
Generalized abdominal pain	0.9	0.4	1.2	1.0

Additional adverse reactions reported from post-marketing experience are included in the table.

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 n known (cannot**

					estimated fro available data)
Infections and infestations	candidiasis, oral candidiasis, vaginal candidiasis, fungal infections	antibiotic-associated colitis, including pseudomembranous colitis*, vaginitis			
Blood and the lymphatic system disorders	thrombocytopenia*, anaemia*†	pancytopenia*, leukopenia*, neutropenia, eosinophilia	sideroblastic anaemia*		myelosuppressio
Immune system disorders			anaphylaxis		
Metabolism and nutrition disorders		hyponatraemia	lactic acidosis*		
Psychiatric disorders	insomnia				
Nervous system disorders	headache, taste perversion (metallic taste), dizziness	convulsions*, peripheral neuropathy*, hypoesthesia, paraesthesia			serotonin syndrome**

Eye disorders		optic neuropathy*, blurred vision*	changes in visual field defect*		optic neuritis loss of vision changes in visu acuity*, changes 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		
Hepatobiliary disorders	abnormal liver function test; increased AST, ALT	increased total bilirubin			

	or alkaline phosphatase				
Skin and subcutaneous tissue disorders	pruritus, rash	angioedema, urticaria, dermatitis bullous, dermatitis, diaphoresis	toxic epidermal necrolysis#, Stevens-Johnson syndrome#, hypersensitivity vasculitis		alopecia
Musculoskeletal and connective tissue disorders			rhabdomyolysis*		
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	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.	Increased sodium or calcium. Decreased non fasting glucose. Increased or decreased chloride. Haematology Increased reticulocyte count. Decreased neutrophils.			

Paediatric Patients:

The safety of linezolid formulations was evaluated in 215 paediatric patients ranging in age from birth through 11 years, and in 248 paediatric 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 paediatric 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.

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

Table 3 shows the incidence of all-causality, treatment-emergent adverse reactions reported in more than 1% of paediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

Table 3. Incidence (%) of Treatment-Emergent Adverse Reactions Occurring in > 1% of Paediatric Patients (and >1 Patient) in Either	**Uncomplicated Skin and Skin Structure Infections***	**All Other Indications †**

Treatment Group in Comparator-Controlled Clinical Trials ADVERSE REACTIONS			
Linezolid (n=248)	**Cefadroxil (n=251)**	**Linezolid (n=215)**	**Vancomycin (n=101)**
Diarrhea	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 linezolid 10 mg/kg by mouth every 12 hours or cefadroxil 15 mg/kg by mouth every 12 hours. Patients 12 years or older received linezolid 600 mg by mouth every 12 hours or cefadroxil 500 mg by mouth every 12 hours.

†Additionally, these adverse events have been observed inpatients from birth through 11 years of age received linezolid 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 paediatric patients treated for uSSSIs, 1.6% of linezolid-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 linezolid-treated and 6.1% of comparator-treated patients.

Laboratory Abnormalities:

Linezolid has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with

Linezolid and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized paediatric 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 Linezolid and 13.4% with vancomycin. In an outpatient study of paediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with Linezolid and 0.4% with cefadroxil. Thrombocytopenia associated with the use of Linezolid 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 Linezolid; the role of linezolid in these events cannot be determined *[see Warning and Precautions (4.4)]*.

Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between Linezolid and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The incidence of adult and paediatric patients with at least one substantially abnormal hematologic or serum chemistry value is presented in Tables 4, 5, 6 and 7.

Table 4. Percent of Adult Patients who Experienced at Least One Substantially Abnormal* Haematology Laboratory Value in Comparator-Controlled Clinical Trials with Linezolid.

Laboratory Assay	**Uncomplicated Skin and Skin Structure Infections**		**All Other Indications**	
	Linezolid 400 mg every 12 hours#	**Clarithromycin 250 mg every 12 hours**	**Linezolid 600 mg every 12 hours**	**All Other Comparators**
Haemoglobin (g/dL)	0.9	0.0	7.1	6.6
Platelet count (×10 /mm)	0.7	0.8	3.0	1.8
WBC (× 10 /mm)	0.2	0.6	2.2	1.3
Neutrophils (×10 /mm)	0.0	0.2	1.1	1.2

*<75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline.

<75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

† Comparators included cefpodoxime proxetil 200 mg by mouth every 12 hours; ceftriaxone 1 g intravenously every 12 hours; dicloxacillin 500 mg by mouth every 6 hours; oxacillin 2 g intravenously every 6 hours; vancomycin 1 g intravenously every 12 hours.

Additionally, these adverse reactions with different strengths have been observed in adult population.

Table 5. Percent of Adult Patients who Experienced at Least One Substantially Abnormal* Serum

Laboratory Assay	**Uncomplicated Skin and Skin Structure Infections**		**All Other Indications**	
	Linezolid 400 mg every 12 hours#	**Clarithromycin 250 mg every 12 hours**	**Linezolid 600 mg every 12 hours**	**All Other Comparators**
AST (U/L)	1.7	1.3	5.0	6.8
ALT (U/L)	1.7	1.7	9.6	9.3
LDH (U/L)	0.2	0.2	1.8	1.5
Alkaline phosphatase (U/L)	0.2	0.2	3.5	3.1
Lipase (U/L)	2.8	2.6	4.3	4.2
Amylase (U/L)	0.2	0.2	2.4	2.0
Total bilirubin (mg/dL)	0.2	0.0	0.9	1.1
BUN (mg/dL)	0.2	0.0	2.1	1.5
Creatinine (mg/dL)	0.2	0.0	0.2	0.6

*>2 × Upper Limit of Normal (ULN) for values normal at baseline;>2 × ULN and >2 × baseline for values abnormal at baseline

Additionally, these adverse reactions with different strengths have been observed in adult population.

†Comparators included cefpodoxime proxetil 200 mg by mouth every 12 hours; ceftriaxone 1 g intravenously every 12 hours; dicloxacillin 500 mg by mouth every 6 hours; oxacillin 2 g intravenously every 6 hours; vancomycin 1 g intravenously every 12 hours.

Table 6. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-Controlled Clinical Trials with Linezolid

Laboratory Assay	**Uncomplicated Skin and Skin Structure Infections**		**All Other Indications**	
	Linezolid 400 mg every 12 hours#	**Clarithromycin 250 mg every 12 hours**	**Linezolid 600 mg every 12 hours**	**All Other Comparators**
Haemoglobin (g/dL)	0.0	0.0	15.7	12.4
Platelet count (× 103/mm3)	0.0	0.4	12.9	13.4
WBC (× 103/mm3)	0.8	0.8	12.4	10.3

Neutrophils (× 103/mm3)	1.2	0.8	5.9	4.3

*<75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline.

if baseline <LLN) of baseline for values abnormal at baseline.

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

‡ Additionally, these adverse events have been observed in patients from birth through 11 years of age received linezolid 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.

Table 7. Percent of Paediatric Patients who Experienced at Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials with linezolid

Laboratory Assay	**Uncomplicated Skin and Skin Structure Infections**	**All Other Indications**

	Linezolid 400 mg every 12 hours#	**Clarithromycin 250 mg every 12 hours**	**Linezolid 600 mg every 12 hours**	**All Other Comparators**
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 × Upper Limit of Normal (ULN) for values normal at baseline; >2 × ULN and >2 (>1.5 for total bilirubin) × baseline for values abnormal at baseline.

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

‡ Additionally, these adverse events have been observed in patients from birth through 11 years of age received linezolid 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.

Post marketing Experience

The following adverse reactions have been identified during post-approval use

of linezolid. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Myelosuppression (including anaemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during post marketing use of linezolid. Peripheral patients treated with linezolid. Lactic acidosis has been reported with the use of linezolid. Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and linezolid. Convulsions have been reported with the use of linezolid. Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens-Johnson syndrome have been reported. Superficial tooth discoloration and tongue discoloration have been reported with the use of linezolid. The tooth discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome. Hypoglycaemia, including symptomatic episodes, has been reported *[see Warnings and Precautions (4.4)]*.

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 hemoperfusion. 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

In a randomized, positive and placebo-controlled crossover thorough QT study, 40 healthy subjects were administered a single linezolid 600 mg dose via a 1-hour IV infusion, a single linezolid 1200 mg dose via a 1-hour IV infusion, placebo, and a single oral dose of positive control. At both the 600 mg and 1200 mg linezolid doses, no significant effect on QTc interval was detected at peak plasma concentration or at any other time.

Microbiology

Mechanism of Action

Linezolid is a synthetic antibacterial agent of the oxazolidinone class, which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The in vitro spectrum of activity of linezolid also includes certain Gram-negative bacteria and anaerobic bacteria. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the

formation of a functional 70S initiation complex, which is essential for bacterial reproduction. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of isolates.

Mechanisms of Resistance

In vitro studies have shown that point mutations in the 23S rRNA are associated with linezolid resistance. Reports of vancomycin-resistant *Enterococcus faecium* becoming resistant to linezolid during its clinical use have been published. There are reports of Staphylococcus aureus (methicillin-resistant) developing resistance to linezolid during clinical use. The linezolid resistance in these organisms is associated with a point mutation in the 23S rRNA (substitution of thymine for guanine at position 2576) of the organism. Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to linezolid. Also, linezolid resistance in staphylococci mediated by the enzyme methyltransferase has been reported. This resistance is mediated by the cfr (chloramphenicol-florfenicol) gene located on a plasmid which is transferable between staphylococci.

Interaction with Other Antimicrobial Drugs

In vitro studies have demonstrated additivity or indifference between linezolid and vancomycin, gentamicin, rifampin, imipenem-cilastatin, aztreonam, ampicillin, or streptomycin.

Linezolid has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections.

<u>Gram-positive bacteria</u>

Enterococcus faecium (vancomycin-resistant isolates only)

Staphylococcus aureus (including methicillin-resistant isolates)

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

The following in vitro data are available, but their clinical significance is unknown. Greater than 90% of the following bacteria exhibit an in vitro MIC less than or equal to the linezolid-susceptible breakpoint for organisms of similar genus shown in Table 8. The safety and effectiveness of linezolid in treating clinical infections due to these bacteria have not been established in adequate and well- controlled clinical trials.

Gram-positive bacteria

Enterococcus faecalis (including vancomycin-resistant isolates)

Enterococcus faecium (vancomycin-susceptible isolates)

Staphylococcus epidermidis (including methicillin-resistant isolates)

Staphylococcus haemolyticus

Viridans group *streptococci*

Gram-negative bacteria

Pasteurella multocida

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-

acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized method (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 8.

Diffusion techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method. This procedure uses paper disks impregnated with 30 mcg linezolid to test the susceptibility of bacteria to linezolid. The disk diffusion interpretive criteria are provided in Table 8.

Table 8. Susceptibility Test Interpretive Criteria for Linezolid

Pathogen	**Susceptibility Interpretive Criteria**					
	Minimal Inhibitory Concentrations (MIC in mcg/mL)			**Disk Diffusion (Zone Diameters in mm)**		
	S	**I**	**R**	**S**	**I**	**R**
Enterococcus spp	≤2	4	≥8	≥23	21–22	≤20
Staphylococcus spp*	≤4	-	≥8	≥21	-	≤20
Streptococcus pneumoniae†	≤2	-	-	≥21	-	-

Streptococcus spp other than *S pneumoniae*†	≤2	-	-	≥21	-	-
Enterococcus spp	≤2	4	≥8	≥23	21–22	≤20

S=susceptible, I=intermediate, R=resistant

* For disk diffusion testing of staphylococcal species, petri plates should be held up to the light source and read with transmitted light. The zone margin should be considered the area showing no obvious, visible growth that can be detected with the unaided eye. Ignore faint growth of tiny colonies that can be detected only with a magnifying lens at the edge of the zone of inhibited growth. Any discernible growth within the zone of inhibition is indicative of resistance. Resistant results obtained by the disk diffusion method should be confirmed using an MIC method.

† The current absence of data on resistant isolates precludes defining any categories other than "Susceptible." Isolates yielding test results suggestive of a "non-susceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the bacteria is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where a high dosage of the drug product can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in

interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard linezolid powder should provide the following range of MIC values noted in Table 9. For the diffusion technique using the 30 mcg linezolid disk, the criteria in Table 9 should be achieved.

Table 9. Acceptable Quality Control Ranges for Linezolid

	Minimum Inhibitory Ranges (MIC in mcg/mL)	**Disk Diffusion Ranges Zone Diameters (mm)**
Enterococcus faecalis ATCC 29212	1 – 4	Not applicable
Staphylococcus aureus ATCC 29213	1 – 4	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	25 – 32
Streptococcus pneumoniae ATCC 49619*	0.25 – 2	25 – 34

* This organism may be used for validation of susceptibility test results when testing Streptococcus spp. other than *S. pneumoniae*.

Clinical Trials

Adults

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a randomized, multi-centre, double-blind trial. Patients were treated for 7 to 21 days. One group received linezolid I.V.

Injection 600 mg every 12 hours, and the other group received vancomycin 1 g every 12 hours intravenously. Both groups received concomitant aztreonam (1 to 2 g every 8 hours intravenously), which could be continued if clinically indicated. There were 203 linezolid-treated and 193 vancomycin-treated patients enrolled in the study. One hundred twenty-two (60%) linezolid-treated patients and 103 (53%) vancomycin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 57% for linezolid-treated patients and 60% for vancomycin-treated patients. The cure rates in clinically evaluable patients with ventilator-associated pneumonia were 47% for linezolid-treated patients and 40% for vancomycin-treated patients. A modified intent-to-treat (MITT) analysis of 94 linezolid-treated patients and 83 vancomycin-treated patients included subjects who had a pathogen isolated before treatment. The cure rates in the MITT analysis were 57% in linezolid-treated patients and 46% in vancomycin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 10.

pathogen	**Cured**	
	Linezolid n/N (%)	**Vancomycin n/N (%)**
Staphylococcus aureus	23/38 (61)	14/23 (61)
Methicillin-resistant *S. aureus*	13/22 (59)	7/10 (70)
Streptococcus pneumonia	9/9 (100)	9/10 (90)

Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections were enrolled in a randomized, multi-centre, double-blind, double-dummy trial comparing study medications administered intravenously followed by medications given orally for a total of 10 to 21 days of treatment. One group of patients received linezolid I.V. Injection 600 mg every 12 hours followed by linezolid Tablets 600 mg every 12 hours; the other group received oxacillin 2 g every 6 hours intravenously followed by dicloxacillin 500 mg every 6 hours orally. Patients could receive concomitant aztreonam if clinically indicated. There were 400 linezolid-treated and 419 oxacillin- treated patients enrolled in the study. Two hundred forty-five (61%) linezolid-treated patients and 242 (58%) oxacillin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 90% in linezolid-treated patients and 85% in oxacillin-treated patients. A modified intent- to-treat (MITT) analysis of 316 linezolid-treated patients and 313 oxacillin-treated patients included subjects who met all criteria for study entry. The cure rates in the MITT analysis were 86% in linezolid-treated patients and 82% in oxacillin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 11.

Table 11. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Complicated Skin and Skin Structure Infections

pathogen	**Cured**	
	Linezolid n/N (%)	**Vancomycin n/N (%)**

Staphylococcus aureus	73/83 (88)	72/84 (86)
Methicillin- resistant *S. aureus*	2/3 (67)	0/0 (-)
Streptococcus agalactiae	6/6 (100)	3/6 (50)
Streptococcus pyogenes	18/26 (69)	21/28 (75)

A separate study provided additional experience with the use of linezolid in the treatment of methicillin- resistant Staphylococcus aureus (MRSA) infections.

This was a randomized, open-label trial in hospitalized adult patients with documented or suspected MRSA infection. One group of patients received linezolid I.V. Injection 600 mg every 12 hours followed by linezolid Tablets 600 mg every 12 hours. The other group of patients received vancomycin 1 g every 12 hours intravenously. Both groups were treated for 7 to 28 days and could receive concomitant aztreonam or gentamicin if clinically indicated. The cure rates in microbiologically evaluable patients with MRSA skin and skin structure infection were 26/33 (79%) for linezolid-treated patients and 24/33 (73%) for vancomycin-treated patients.

Diabetic Foot Infections

Adult diabetic patients with clinically documented complicated skin and skin structure infections ("diabetic foot infections") were enrolled in a randomized (2:1 ratio), multi-centre, open-label trial comparing study medications administered intravenously or orally for a total of 14 to 28 days of treatment. One group of patients received linezolid 600 mg every 12 hours intravenously or orally; the other group received ampicillin/sulbactam 1.5 to 3 g intravenously or amoxicillin/clavulanate 500 to 875 mg every 8 to 12 hours

orally. In countries where ampicillin/sulbactam is not marketed, amoxicillin/clavulanate 500 mg to 2 g every 6 hours was used for the intravenous regimen. Patients in the comparator group could also be treated with vancomycin 1 g every 12 hours intravenously if MRSA was isolated from the foot infection. Patients in either treatment group who had Gram-negative bacilli isolated from the infection site could also receive aztreonam 1 to 2 g every 8–12 hours intravenously. All patients were eligible to receive appropriate adjunctive treatment methods, such as debridement and off-loading, as typically required in the treatment of diabetic foot infections, and most patients received these treatments. There were 241 linezolid-treated and 120 comparator-treated patients in the intent-to- treat (ITT) study population. Two hundred twelve (86%) linezolid-treated patients and 105 (85%) comparator-treated patients were clinically evaluable. In the ITT population, the cure rates were 68.5% (165/241) in linezolid-treated patients and 64% (77/120) in comparator-treated patients, where those with indeterminate and missing outcomes were considered failures. The cure rates in the clinically evaluable patients (excluding those with indeterminate and missing outcomes) were 83% (159/192) and 73% (74/101) in the linezolid- and comparator-treated patients, respectively. A critical post-hoc analysis focused on 121 linezolid-treated and 60 comparator-treated patients who had a Gram-positive pathogen isolated from the site of infection or from blood, who had less evidence of underlying osteomyelitis than the overall study population, and who did not receive prohibited antimicrobials.

Based upon that analysis, the cure rates were 71% (86/121) in the linezolid-treated patients and 63% (38/60) in the comparator-treated

patients. None of the above analyses were adjusted for the use of adjunctive therapies. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 12.

Table 12 Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Diabetic Foot Infections

Pathogen	**Cured**	
	Linezolid n/N (%)	**Comparator n/N (%)**
Staphylococcus aureus	49/63 (78)	20/29 (69)
Methicillin-resistant S. aureus	12/17 (71)	2/3 (67)
Streptococcus agalactiae	25/29 (86)	9/16 (56)

Vancomycin-Resistant Enterococcal Infections

Adult patients with documented or suspected vancomycin-resistant enterococcal infection were enrolled in a randomized, multi-centre, double-blind trial comparing a high dose of linezolid (600 mg) with a low dose of linezolid (200 mg) given every 12 hours either intravenously (IV) or orally for 7 to 28 days.

Patients could receive concomitant aztreonam or aminoglycosides. There were 79 patients randomized to high-dose linezolid and 66 to low-dose

linezolid. The intent-to-treat (ITT) population with documented vancomycin-resistant enterococcal infection at baseline consisted of 65 patients in the high- dose arm and 52 in the low-dose arm.

The cure rates for the ITT population with documented vancomycin-resistant enterococcal infection at baseline are presented in Table 13 by source of infection. These cure rates do not include patients with missing or indeterminate outcomes. The cure rate was higher in the high dose arm than in the low-dose arm, although the difference was not statistically significant at the 0.05 level.

Table 13. Cure Rates at the Test-of-Cure Visit for ITT Adult Patients with Documented Vancomycin-Resistant Enterococcal Infections at Baseline

Source of Infection	**Cured**	
	Linezolid 600 mg every 12 hours n/N (%)	**Linezolid 200 mg every 12 hours n/N (%)**
Any site	39/58 (67)	24/46 (52)
Source of Infection	**Cured**	
	Linezolid 600 mg every 12 hours n/N (%)	**Linezolid 200 mg every 12 hours n/N (%)**
Any site with associated bacteraemia	10/17 (59)	4/14 (29)
Bacteraemia of unknown origin	5/10 (50)	2/7 (29)
Skin and skin structure	9/13 (69)	5/5 (100)

Urinary tract	12/19 (63)	12/20 (60)
Pneumonia	2/3 (67)	0/1 (0)
Other*	11/13 (85)	5/13 (39)

* Includes sources of infection such as hepatic abscess, biliary sepsis, necrotic gall bladder,
peri colonic abscess, pancreatitis, and catheter- related infection.

5.1.2.2 Paediatric Patients

Infections due to Gram-positive Bacteria

A safety and efficacy study provided experience on the use of linezolid in paediatric patients for the treatment of nosocomial pneumonia, complicated skin and skin structure infections, and other infections due to Gram-positive bacterial pathogens, including methicillin-resistant and susceptible Staphylococcus aureus and vancomycin-resistant *Enterococcus faecium*. Paediatric patients ranging in age from birth through 11 years with infections caused by the documented or suspected Gram-positive bacteria were enrolled in a randomized, open-label, comparator-controlled trial. One group of patients received linezolid I.V. Injection 10 mg/kg every 8 hours followed by linezolid for Oral Suspension 10 mg/kg every 8 hours. A second group received vancomycin 10 to 15 mg/kg intravenously every 6 to 24 hours, depending on age and renal clearance. Patients who had confirmed VRE infections were placed in a third arm of the study and received linezolid 10 mg/kg every 8 hours intravenously and/or orally. All patients were treated for a total of 10 to 28 days and could receive concomitant Gram-negative antibiotics if clinically indicated. In the intent-to-treat (ITT) population, there were 206 patients randomized to linezolid and 102

patients randomized to vancomycin. The cure rates for ITT, MITT, and clinically evaluable patients are presented in Table 14. After the study was completed, 13 additional patients ranging from 4 days through 16 years of age were enrolled in an open-label extension of the VRE arm of the study. Table 15 provides clinical cure rates by pathogen for microbiologically evaluable patients including microbiologically evaluable patients with vancomycin-resistant *Enterococcus faecium* from the extension of this study.

Table 14. Cure Rates at the Test-of-Cure Visit for Intent-to-Treat, Modified Intent-to Treat, and Clinically Evaluable Pediatric Patients for the Overall Population and by Select Baseline Diagnosis

Population	**ITT**		**MITT***		**Clinically Evaluable**	
	Linezolid n/N (%)	**Vancomycin n/N (%)**	**linezolid n/N (%)**	**Vancomycin n/N (%)**	**linezolid n/N (%)**	**Vancomycin n/N (%)**
Any diagnosis	150/186	69/83 (83)	86/108	44/49 (90)	106/117	49/54 (91)
Complicated skin and skin structure infections	(81) 61/72 (85)	31/34 (91)	(80) 37/43 (86)	22/23 (96)	(91) 46/49 (94)	26/27 (96)
Nosocomial pneumonia	13/18 (72)	11/12 (92)	5/6 (83)	4/4 (100)	7/7 (100)	5/5 (100)

* MITT = ITT patients with an isolated Gram- positive pathogen at baseline

Table 15. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Pediatric Patients with Infections due to Gram-positive Pathogens

Pathogen	**Microbiologically Evaluable**	
	Linezolid n/N (%)	**Vancomycin n/N (%)**
Vancomycin-resistant *Enterococcus faecium*	6/8 (75) *	0/0 (-)
Staphylococcus aureus	36/38 (95)	23/24 (96)
Methicillin-resistant *S. aureus*	16/17 (94)	9/9 (100)
Streptococcus pyogenes	2/2 (100)	1/2 (50)

* Includes data from 7 patients enrolled in the open- label extension of this study.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of linezolid in adults after single and multiple oral doses are summarized in Table 16. Plasma concentrations of linezolid at steady state after oral doses of 600 mg given every 12 hours are shown in Figure 1.

Table 16 Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	**Cmax mcg/mL**	**Cmin mcg/mL**	**Tmax hrs**	**AUC * mcg·h/mL**	**t1/2 hrs**	**CL mL/min**
600 mg tablet		---				

single dose	12.70 (3.96)		1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
every 12 hours	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)

C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; T_{max} = Time to C_{max}; AUC = Area under concentration-time curve; $t_{1/2}$ = Elimination half-life; CL = Systemic clearance

* AUC for single dose = $AUC_{0-\infty}$; for multiple dose = $AUC_{0-\tau}$

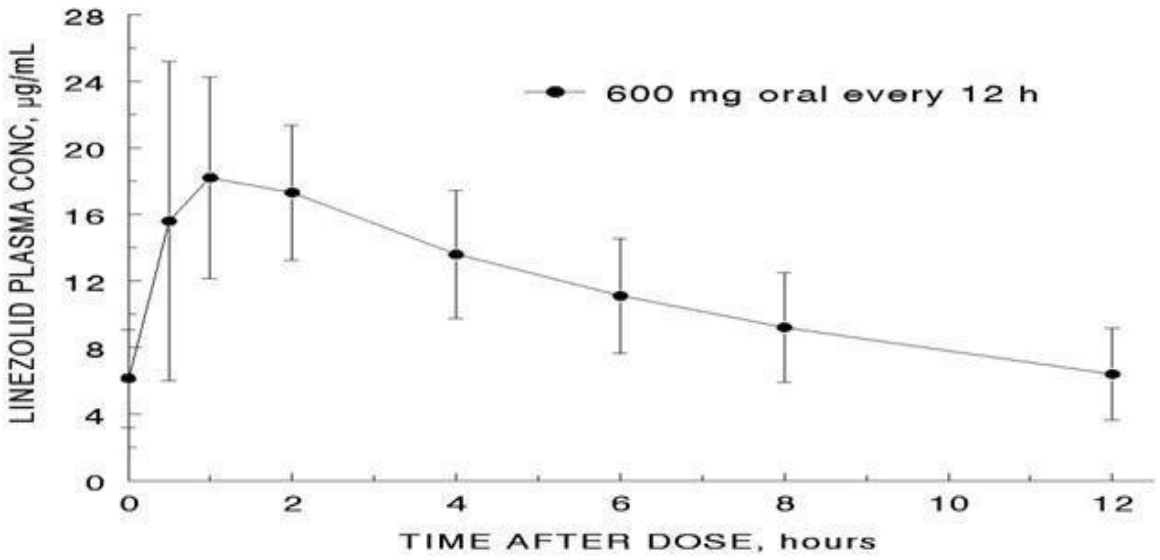

Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-State Following Oral Dosing Every 12 Hours (Mean ± Standard Deviation, n=16)

Absorption

Linezolid is extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, linezolid may be given orally without dose adjustment.

Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as $AUC_{0-\infty}$ is similar under both conditions.

Dissolution

Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well- perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent. The volume of distribution of linezolid at steady state averaged 40 to 50 litres in healthy adult volunteers.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase 1 volunteer studies following multiple dosing of linezolid. The ratio of linezolid in saliva relative to plasma was 1.2 to 1 and the ratio of linezolid in sweat relative to plasma was 0.55 to 1.

Metabolism

Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxy acetic acid metabolite (A), and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a non-enzymatic chemical oxidation mechanism in vitro. In vitro studies have demonstrated

that linezolid is minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of linezolid is not fully understood.

Excretion

Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. Under steady- state conditions, approximately 30% of the dose appears in the urine as linezolid, 40% as metabolite B, and 10% as metabolite A. The mean renal clearance of linezolid is 40 mL/min which suggests net tubular reabsorption. Virtually no linezolid appears in the faeces, while approximately 6% of the dose appears in the faeces as metabolite B, and 3% as metabolite A.

A small degree of nonlinearity in clearance was observed with increasing doses of linezolid, which appears to be due to lower renal and non-renal clearance of linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

Special population

Geriatric patients

The pharmacokinetics of linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

Paediatric patients

The pharmacokinetics of linezolid following a single intravenous dose were investigated in paediatric 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 paediatric patients ranging in age from 1 week through 12 years. The pharmacokinetic parameters of linezolid are summarized in Table 17 for the paediatric populations studied and healthy adult subjects after administration of single intravenous doses.

The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age in paediatric 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 paediatric 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 paediatric age groups as compared with adults.

Similar mean daily AUC values were observed in paediatric 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 paediatric patients up to 11 years of age should be 10 mg/kg every 8 hours. Paediatric patients 12 years and older should receive 600 mg every 12 hours.

Table 17. Pharmacokinetic Parameters of Linezolid in Paediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

	Cmax		**AUC***	**t 1/2**	**CL**
		Vss L/kg			
Age Group	**mcg/mL**		**mcg·h/mL**	**hrs**	**mL/min/kg**
Neonatal Patients					
	12.7	0.81		5.6	
Pre-term†			108 (47%)		2.0 (52%)
	(30%)	(24%)		(46%)	
‡	[9.6,	[0.43,		[2.4,	
< 1 week (N=9)			[41, 191]		[0.9, 4.0]
	22.2]	1.05]		9.8]	
	11.5	0.78		3.0	
Full-term§			55 (47%)		3.8 (55%)

	(24%)	(20%)		(55%)	
‡	[8.0,	[0.45,		[1.3,	
< 1 week (N=10)			[19, 103]		[1.5, 8.8]
	18.3]	0.96]		6.1]	
	12.9	0.66		1.5	
Full-term§			34 (21%)		5.1 (22%)
	(28%)	(29%)		(17%)	
≥ 1 week to ≤ 28 days	[7.7,	[0.35,		[1.2,	
			[23, 50]		[3.3, 7.2]
(N=10) ‡	21.6]	1.06]		1.9]	
Infant Patients					
	11.0 (27%)	0.79 (26%)		1.8 (28%)	
			33 (26%)		5.4 (32%)
	[7.2,	[0.42,		[1.2,	
> 28 days to < 3 Months			[17, 48]		[3.5, 9.9]
‡	18.0]	1.08]		2.8]	
(N=12)					
Paediatric Patients					
	15.1	0.69		2.9	
	(30%)	(28%)	58 (54%)	(53%)	3.8 (53%)
3 months through 11					

‡ [6.8, [0.31, [19, 153] [0.9, [1.0, 8.5] years					
	36.7]	1.50]		8.0]	
(N=59)					
				4.1	
Adolescent Subjects and 16.7		0.61			
Patients	(24%)	(15%)	95 (44%)		2.1 (53%)
12 through 17 years ¶[9.9,		[0.44,	[32, 178]	(46%)	[0.9, 5.2]
				[1.3,	
(N=36)	28.9]	0.79]			
				8.1]	
	12.5	0.65		4.9	
Adult Subjects#	(21%)	(16%)	91 (33%)	(35%)	1.7 (34%)
(N= 29)	[8.2,	[0.45,	[53, 155]	[1.8,	[0.9, 3.3]
	19.3]	0.84]		8.3]	

C_{max} = Maximum plasma concentration; Vss= Volume of distribution; AUC = Area under concentration-time curve.

t1/2 = Apparent elimination half-life; CL = Systemic clearance normalized for body weight

* 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)

‡ Dose of 10 mg/kg

§ In this data set, "full- term" is defined as ≥34 weeks gestational age

¶ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg

Dose normalized to 600 mg

Gender

Females have a slightly lower volume of distribution of linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. After a 600-mg dose, mean oral clearance is approximately 38% lower in females than in males. However, there are no significant gender differences in mean apparent elimination-rate constant or half-life. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

Renal Impairment

The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal impairment; however, the two primary metabolites of linezolid accumulate in patients with renal impairment, with the amount of accumulation increasing with the severity of renal dysfunction (see Table 18). The pharmacokinetics of linezolid and its two

metabolites have also been studied in patients with end-stage renal disease (ESRD) receiving haemodialysis. In the ESRD study, 14 patients were dosed with linezolid 600 mg every 12 hours for 14.5 days (see Table 19). Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal impairment. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal impairment should be weighed against the potential risks of accumulation of these metabolites. Both linezolid and the two metabolites are eliminated by haemodialysis. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Approximately 30% of a dose was eliminated in a 3-hour haemodialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after haemodialysis.

Table 18. Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Patients with Varying Degrees of Renal Impairment After a Single 600 mg Oral Dose of Linezolid

Parameter	**Healthy Subjects CLCR > 80 mL/min**	**Moderate Renal Impairment 30 < CLCR < 80 mL/min**	**Severe Renal Impairment 10 < CLCR < 30 mL/min**	
LINEZOLID				
AUC0–∞, mcg h/mL	110 (22)	128128 (53) (53)	127 (66)	
	t1/2, hours	6.4 (2.2)	6.1 (1.7)	7.1
METABOLITE A				(3.7)

AUC0–48, mcg h/mL	7.6 (1.9)	11.7 (4.3)	56.5 (30.6)
t1/2, hours	6.3 (2.1)	6.6 (2.3)	9.0 (4.6)
METABOLITE B*			
AUC0–48, mcg h/mL	30.5 (6.2)	51.1 (38.5)	203 (92)
t1/2, hours	6.6 (2.7)	9.9 (7.4)	11.0 (3.9)

* Metabolite B is the major metabolite of linezolid.

Table 19 Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Subjects with End-Stage Renal Disease (ESRD) After the Administration of 600 mg Linezolid Every 12 Hours for 14.5 Days

Parameter	**ESRD Subjects***
LINEZOLID	
$AUC_{0–12}$, mcg h/mL (after last dose)	181 (52.3)
$t_{1/2}$, h (after last dose)	8.3 (2.4)
METABOLITE A	
$AUC_{0–12}$, mcg h/mL (after last dose)	153 (40.6)
$t_{1/2}$, h (after last dose)	15.9 (8.5)
METABOLITE B†	
$AUC_{0–12}$, mcg h/mL (after last dose)	356 (99.7)
$t_{1/2}$, h (after last dose)	34.8 (23.1)

* Between haemodialysis sessions

† Metabolite B is the major metabolite of linezolid.

Hepatic Impairment

The pharmacokinetics of linezolid are not altered in patients (n=7) with mild-to-moderate hepatic impairment (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for

patients with mild-to-moderate hepatic impairment. The pharmacokinetics of linezolid in patients with severe hepatic impairment have not been evaluated.

Drug Interactions

Drugs Metabolized by Cytochrome P450

Linezolid is not an inducer of cytochrome P450 (CYP450) in rats. In addition, linezolid does not inhibit the activities of clinically significant human CYP isoforms (e.g., 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, linezolid is not expected to affect the pharmacokinetics of other drugs metabolized by these major enzymes. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Antibiotics

Aztreonam: The pharmacokinetics of linezolid or aztreonam are not altered when administered together.

Gentamicin: The pharmacokinetics of linezolid or gentamicin are not altered when administered together.

Antioxidants

The potential for drug-drug interactions with linezolid and the antioxidants Vitamin C and Vitamin E was studied in healthy volunteers. Subjects were administered a 600 mg oral dose of linezolid on Day 1, and another 600 mg

dose of linezolid on Day 8. On Days 2–9, subjects were given either Vitamin C (1000 mg/day) or Vitamin E (800 IU/ day). The $AUC_{0-\infty}$ of linezolid increased 2.3% when co-administered with Vitamin C and 10.9% when co-administered with Vitamin E. No linezolid dose adjustment is recommended during co-administration with Vitamin C or Vitamin E.

Strong CYP 3A4 Inducers

Rifampin: The effect of rifampin on the pharmacokinetics of linezolid was evaluated in a study of 16 healthy adult males. Volunteers were administered oral linezolid 600 mg twice daily for 5 doses with and without rifampin 600 mg once daily for 8 days. Co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid C_{max} [90% CI, 15% – 27%] and a 32% decrease in linezolid AUC_{0-12} [90% CI, 27% – 37%]. The clinical significance of this interaction is unknown. The mechanism of this interaction is not fully understood and may be related to the induction of hepatic enzymes. Other strong inducers of hepatic enzymes (e.g. carbamazepine, phenytoin, phenobarbital) could cause a similar or smaller decrease in linezolid exposure.

Monoamine Oxidase Inhibition

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

Adrenergic Agents

Some individuals receiving linezolid may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response.

Tyramine: A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content.

Pseudoephedrine HCl or phenylpropanolamine HCl: A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects. A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg every 12 hours for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments. Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2 to 3 hours after the second dose of PPA or PSE and returned to baseline 2 to 3 hours after peak. The results of the PPA study follow, showing the mean

(and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg (range: 20–52 mm Hg) and 38 mm Hg (range: 18–79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively.

Serotonergic Agents

Dextromethorphan: 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

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Neither mutagenic nor clastogenic potential was found in a battery of tests including assays for mutagenicity (Ames bacterial reversion and CHO cell mutation), an in vitro unscheduled DNA synthesis (UDS) assay, an in vitro chromosome aberration assay in human lymphocytes, and an in vivo mouse micronucleus assay.

Linezolid did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ≥ 50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). The reversible fertility effects were mediated through altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. Epithelial cell hypertrophy and hyperplasia in the epididymis was observed in conjunction with decreased fertility. Similar epididymal changes were not seen in dogs.

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-fold greater than mean AUCs observed in paediatric 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.

Animal Toxicology and/or Pharmacology

Target organs of linezolid toxicity were similar in juvenile and adult rats and dogs. Dose- and time- dependent myelosuppression, as evidenced by bone marrow hypocellularity/decreased haematopoiesis, decreased extramedullary haematopoiesis in spleen and liver, and decreased levels of circulating erythrocytes, leukocytes, and platelets have been seen in animal studies. Lymphoid depletion occurred in thymus, lymph nodes, and spleen. Generally, the lymphoid findings were associated with anorexia, weight loss, and suppression of body weight gain, which may have contributed to the observed effects.

In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was evident in 2 male rats 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 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.

These effects were observed at exposure levels that are comparable to those observed in some human subjects. The hematopoietic and lymphoid effects

were reversible, although in some studies, reversal was incomplete within the duration of the recovery period.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose Monohydrate (Pharmat 200M)

Polacrilin Potassium (Kyron T-314)

Hypromellose (Methocel- E5)

Colloidal Silica Dioxide (Aerosil 200)

Magnesium Stearate

Hydroxy propyl methyl cellulose, polyethylene glycol, titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Do not store above 30°C. Protected from moisture

6.5 Nature and Content of container

- 10 Tablets in Clear PVC/PVDC blister pack: The primary packs are blister cards of 10 tablets (comprised of PVC/PVDC FOIL 180MM CLEAR 40GSM.Foil sealed with BLISTER AL FOIL 180MM 0.025MM). Such 10 blisters kept in a carton with one pack insert (if any). and
- 10 Tablets Clear PVC blister pack: The primary packs are blister cards of 10 tablets (comprised of PVC FOIL 180MM CLEAR. Foil sealed with BLISTER AL FOIL 180MM 0.025MM). Such 10 blisters kept in a carton with one pack insert (if any). and
- 20 Tablets in HDPE Bottle**:** Tablets are packed in 40ML ROUND Opaque WHITE

HDPE BOTTLE, 33 NECK and closed with 33 MM Polypropylene WHITE SCREW CAP WITH IHS LINER and sealed with induction sealing. It is labelled.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. Marketing Authorization Holder

Lupin Limited

Kalpataru Inspire, 3rd Floor, Off Western Express Highway,

Santacruz (East), Mumbai 400055, India.

8. Marketing Authorization Number

CTD9618

9. Date of first authorization/renewal of the authorization

03/02/2023

10. Date of revision of the text

10/05/2025