For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

LINOX 600

1. Generic Name

Linezolid Tablets I.P. 600 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Linezolid I.P. ……... 600mg

Excipients …. q.s.

Colour: Titanium Dioxide I.P.

The Excipients used are Lactose Monohydrate, Starch, Sodium Starch Glycollate, Povidone K- 30, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Isopropyl Alcohol, Methylene Chloride, Opadry Y-1-7000

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: 600mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

For the treatment of osteomyelitis in adults, for the treatment of complicated/uncomplicated skin & skin structure infection, community acquired pneumonia.

4.2 Posology and Method of Administration

Posology

Linezolid film-coated tablets may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to either oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as linezolid has an oral 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.

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

The dose recommendation for the tablets is as follows:

Infections	Dosage	Duration of treatment
Nosocomial pneumonia	600 mg twice daily	10-14 Consecutive days
Community acquired pneumonia	600mg twice daily	10-14 Consecutive days
Complicated skin and soft tissue infections	600 mg twice daily	10-14 Consecutive days

Paediatric population: There are insufficient data on the safety and efficacy of linezolid in children and adolescents (< 18 years old) to establish dosage recommendations. Therefore, until further data are available, use of linezolid in this age group is not recommended.

Elderly patients: No dose adjustment is required.

Patients with renal insufficiency: No dose adjustment is required.

Patients with severe renal insufficiency (i.e. CLCR < 30 ml/min): No dose adjustment is required. Due to the unknown clinical significance of higher exposure (up to 10-fold) to the two primary metabolites of linezolid in patients with severe renal insufficiency, linezolid should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

As approximately 30% of a linezolid dose is removed during 3 hours of 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 hepatic insufficiency: No dose adjustment is required. However, there are limited clinical data, and it is recommended that linezolid should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk.

Method of administration:

The recommended linezolid dosage should be administered intravenously or orally twice daily. Route of administration: Oral use.

The film-coated tablets may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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, 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, breastfeeding should be discontinued prior to and throughout administration.

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. 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.

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 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.

Concomitant administration of linezolid and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition.

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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.

Use with tyramine-rich foods

Patients should be advised against consuming large amounts of tyramine rich foods.

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.

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.

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.

Lactose: The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs Interactions

Linezolid should be used cautiously when co-administered with:

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.

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 with linezolid.

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, management of patients for whom treatment with linezolid and serotonergic agents is essential.

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.

Buprenorphine/opioids

Buprenorphine/opioids as the risk of serotonin syndrome, a potentially life- threatening condition, is increased.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Pregnancy

There are no adequate data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity. 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.

Breastfeeding

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

Fertility

In animal studies, linezolid caused a reduction in fertility.

4.7 Effects on Ability to Drive and Use Machines

Patients should be warned about the potential for dizziness or symptoms of visual impairment 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 that occurred at frequencies ≥ 0.1% or considered to be serious in 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	Candidiasis,	Vaginitis	Antibiotic-		
infestations	oral candidiasis, vaginal candidiasis, fungal infections		associated colitis, including pseudomembranous colitis*		
Blood and the lymphatic system disorders	Anaemia*†	Leucopenia*, neutropenia, thrombocytopenia* eosinophilia	Pancytopenia*		Myelosuppression*, sideroblastic anaemia*
Immune system disorders					Anaphylaxis

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)
Metabolism and nutrition disorders		Hyponatraemia Hypoglycemia			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	Superficial tooth discolouration Black hairy tongue		

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)
		or disorder			
Hepato-biliary	Abnormal liver function	Increased total			
disorders	test; increased AST, ALT or alkaline phosphatase	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
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	<u>Chemistry</u> Increased LDH, creatine kinase, lipase, amylase or non fasting glucose.	<u>Chemistry</u> Increased sodium or calcium. Decreased non fasting glucose. Increased or decreased			

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)
	Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate. <u>Haematology</u> Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.	chloride. <u>Haematology</u> 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 patient's 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.

<u>Paediatric population</u>

Safety data from clinical studies based on more than 500 paediatric patients (from birth to 17 years) do not indicate that the safety profile of linezolid for paediatric patients differs from that for adult patients.

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

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 Mechanism of Action

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.

5.2 Pharmacodynamic Properties

General Properties

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

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for Minimum inhibitory concentration (MIC) are presented below.

Table: EUCAST clinical MIC breakpoints for linezolid (2016-01-01, v 6.0)

	Susceptible	**Resistant**
Enterococcus spp.	≤ 4mg/L	>4mg/L
Staphylococcus spp.	≤ 4mg/L	>4mg/L
Streptococcus groups A, B, C and G	≤ 2mg/L	>4mg/L
Streptococcus pneumoniae	≤ 2mg/L	>4mg/L

	Susceptible	Resistant
Corynebacterium spp.	≤ 2mg/L	>2mg/L
Non-species related breakpoints*	≤ 2mg/L	>4mg/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 gram-positive 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).

5.3 Pharmacokinetic Properties

Linezolid primarily contains (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 and absorption from the oral suspension is similar to that achieved with the film-coated tablets.

Plasma linezolid C_{max} and C_{min} (mean and [SD]) at steady state following twice daily intravenous dosing of 600 mg have been determined to be 15.1 [2.5] mg/l and 3.68 [2.68] mg/l, respectively.

In another study following oral dosing of 600 mg twice daily to steady-state, C_{max} and C_{min} were determined to be 21.2 [5.8] mg/l and 6.15 [2.94] mg/l, respectively. Steady-state conditions are achieved by the second day of dosing.

Distribution

Volume of distribution at steady-state averages at about 40-50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31% and is not concentration dependent.

Linezolid concentrations have been determined in various fluids from a limited number

of subjects in volunteer studies following multiple dosing. The ratio of linezolid in saliva and sweat relative to plasma was 1.2:1.0 and 0.55:1.0, respectively. The ratio for epithelial lining fluid and alveolar cells of the lung was 4.5:1.0 and 0.15:1.0, when measured at steady-state 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.

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

Patients with renal insufficiency: After single doses of 600 mg, there was a 7-8-fold increase in exposure to the two primary metabolites of linezolid in the plasma of patients with severe renal insufficiency (i.e. creatinine clearance < 30 ml/min). However, there was no increase in AUC of parent drug. Although there is some removal of the major metabolites of linezolid by 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.

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

Children and adolescents (< 18 years old): There are insufficient data on the safety and efficacy of linezolid in children and adolescents (< 18 years old) and therefore, use of linezolid in this age group is not recommended. Further studies are needed to establish safe and effective dosage recommendations. Pharmacokinetic studies indicate that after single and multiple doses in children (1 week to 12 years), linezolid clearance (based on kg body weight) was greater in paediatric patients than in adults but decreased with increasing age.

In children 1 week to 12 years old, administration of 10 mg/kg every 8 hours daily gave exposure approximating to that achieved with 600 mg twice daily in adults.

In neonates up to 1 week of age, the systemic clearance of linezolid (based on kg body weight) increases rapidly in the first week of life. Therefore, neonates given 10 mg/kg every 8 hours daily will have the greatest systemic exposure on the first day after delivery. However, excessive accumulation is not expected with this dosage regimen during the first week of life as clearance increases rapidly over that period.

In adolescents (12 to 17 years old), linezolid pharmacokinetics were similar to that in adults following a 600mg dose. Therefore, adolescents administered 600 mg every 12 hours daily will have similar exposure to that observed in adults receiving the same dosage.

In paediatric patients with ventriculoperitoneal shunts who were administered linezolid 10mg/kg either 12 hourly or 8 hourly, variable cerebrospinal fluid (CSF) linezolid concentrations were observed following either single or multiple dosing of linezolid. Therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empirical treatment of paediatric patients with central nervous system infections is not recommended.

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

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

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those expected in humans. In sexually mature animals these effects were reversible. 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.

Reproductive toxicity studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4 times or equivalent, respectively, to those expected in humans. The same linezolid concentrations caused maternal toxicity in mice and were related to

increased embryo death including total litter loss, decreased fetal body weight and an exacerbation of the normal genetic predisposition to sternal variations in the strain of mice. In rats, slight maternal toxicity was noted at exposures lower than expected clinical exposures. Mild fetal toxicity, manifested as decreased fetal body weights, reduced ossification of sternebrae, reduced pup survival and mild maturational delays were noted. When mated, these same pups showed evidence of a reversible dose-related increase in pre-implantation loss with a corresponding decrease in fertility. 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.

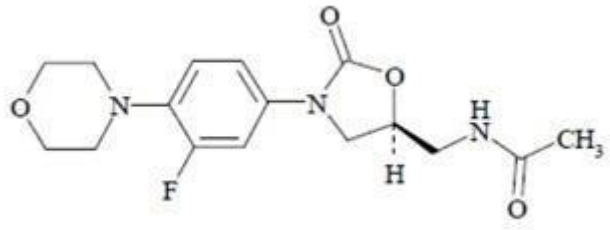
Linezolid produced reversible myelosuppression in rats and dogs.

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 in the standard battery of studies.

7. DESCRIPTION

Linezolid Tablets contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. It is a white to off-white, crystalline powder. The chemical name for linezolid is N-[[(5S)-3-[3-fluoro-4-(4- morpholinyl) phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide. The empirical formula is $C_{16}H_{20}FN_3O_4$. Its molecular weight is 337.4, and its chemical structure is represented below:



Linezolid Tablet for oral administration contains 600 mg linezolid as a film-coated compressed tablet. Linezolid is a soluble in chloroform and slightly soluble in methanol. The Excipients used are Lactose Monohydrate, Starch, Sodium Starch Glycollate, Povidone K-30, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Isopropyl Alcohol,

Methylene Chloride, Opadry Y-1-7000.

Linezolid Tablets are white, capsule shaped, biconvex, film coated tablets with score on one side and plain on other side.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

LINOX 600 is available in 10 blister Strips of 10 tablets each.

8.4 Storage and Handing Instructions

Store in a dry place at temperature not exceeding 30°C, protect from light.

9. PATIENT COUNSELLING INFORMATION

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. DETAILS OF MANUFACTURER

TORRENT PHARMACEUTICALS LTD

32 No. Middle Camp, NH-10,

East district, Gangtok, Sikkim-737135.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg. Lic. No.: M/563/2010 issued on 06.12.2021.

12. DATE OF REVISION

APR 2026

MARKETED BY

TORRENT PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/LINOX 600 mg/APR-2026/03/PI