

LINOX 600

1. Generic Name

Linezolid Tablets I.P. 600 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated Tablets 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 Tablets

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

Dose: As directed by the Physician.

Posology

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.

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

The dose recommendation for the solution for infusion and the tablets/granules for oral suspension are identical are as follows:

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

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

As approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by haemodialysis, but the concentrations of these metabolites are still very considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Therefore, linezolid should be used with special caution in patients with severe renal insufficiency who are undergoing dialysis and only when the anticipated benefit is considered to outweigh the theoretical risk.

To date, there is no experience of linezolid administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than haemodialysis).

Patients with 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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent. In cases of suspected or verified antibiotic-associated colitis, discontinuation of linezolid may be warranted. Appropriate management measures should be instituted.

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.

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

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 C_{max} and AUC by a mean 21% [90% CI, 15, 27] and a mean 32% [90% CI, 27, 37], respectively. The mechanism of this interaction and its clinical significance are unknown.

Warfarin

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

4.6 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

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those expected in humans. In dogs treated for 1 month, changes in the weights of prostate, testes and epididymis were apparent.

It is not known whether these findings have an impact on human 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 $\geq 0.1\%$ 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.

Approximately 22% of patients experienced adverse reactions; those most commonly reported were headache (2.1%), diarrhoea (4.2%), nausea (3.3%) and candidiasis (particularly oral [0.8%] and vaginal [1.1%] candidiasis, see table below). 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); Not known (cannot be estimated from the available data)

System Organ Class	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Very Rare ($< 1/10,000$)	Frequency not known (cannot be estimated from available data)
Infections and infestations	Candidiasis, oral candidiasis, vaginal candidiasis, fungal infections	Vaginitis			Antibiotic-associated colitis, including pseudomembranous colitis*
Blood and the lymphatic system disorders		Leucopenia*, neutropenia, thrombocytopenia*, eosinophilia			Myelosuppression*, pancytopenia*, anaemia* [†] , sideroblastic anaemia*
Immune system disorders					Anaphylaxis
Metabolism and nutrition disorders					Lactic acidosis*, hyponatraemia

Psychiatric disorders		Insomnia		
Nervous system disorders	Headache, taste perversion (metallic taste)	Dizziness, hypoaesthesia, paraesthesia		Serotonin syndrome**, convulsions*, peripheral neuropathy*
Eye disorders		Blurred vision*		Optic neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*, changes in visual field defect*
Ear and labyrinth disorders		Tinnitus		
Cardiac disorders			Arrhythmia (tachycardia)	
Vascular disorders		Hypertension, phlebitis, thrombophlebitis	Transient ischaemic attacks	
Gastrointestinal disorders	Diarrhoea, nausea, vomiting.	Pancreatitis, gastritis, localised or general abdominal pain, constipation, dry mouth, dyspepsia, glossitis, loose stools, stomatitis, tongue discoloration or disorder		Superficial tooth discoloration
Hepatobiliary disorders	Abnormal liver function test; increased	Increased total bilirubin		

	AST, ALT or alkaline phosphatase				
Skin and subcutaneous tissue disorders		Urticaria, dermatitis, diaphoresis, pruritus, rash			Bullous disorders such as those described as Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, alopecia
Renal and urinary disorders	Increased BUN	Polyuria, increased creatinin	Renal failure		
Reproductive system and breast disorders		Vulvovaginal disorder			
General disorders and administration site conditions		Chills, fatigue, fever, injection site pain, increased thirst, localised pain			
Investigations	<u>Chemistry</u> Increased LDH, creatine kinase, lipase, amylase or non-fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate.	<u>Chemistry</u> Increased sodium or calcium. Decreased non fasting glucose. Increased or decreased chloride. <u>Haematology</u> Increased reticulocyte count. Decreased neutrophils.			

	<u>Haematology</u> Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.				
--	---	--	--	--	--

* See Special warnings and precautions for use.

** See Contraindications and Interaction with other medicinal products and other forms of interaction

† 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, less than 0.1% of the patients reported anaemia. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for >28 days. The proportion of cases reporting drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for >28 days.

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 side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

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

Pharmacotherapeutic group: Other antibacterials, ATC code: J01XX08

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

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and enterococci are Susceptible ≤ 4 mg/L and Resistant >4 mg/L. For streptococci (including *S. pneumoniae*) the breakpoints are Susceptible ≤ 2 mg/L and Resistant >4 mg/L.

Non-species related MIC breakpoints are susceptible ≤ 2 mg/L and Resistant > 4 mg/L. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that have not been given a specific breakpoint and not for those species where susceptibility testing is not recommended.

Susceptibility

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

Category
<u>Susceptible organisms</u>
Gram positive aerobes:
<i>Enterococcus faecalis</i>
<i>Enterococcus faecium</i> *
<i>Staphylococcus aureus</i> *
Coagulase negative staphylococci
<i>Streptococcus agalactiae</i> *

*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 C_{max}, 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 C_{max} 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.

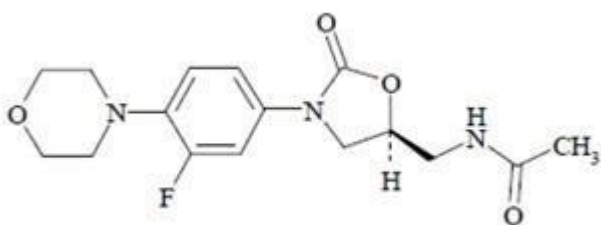
Linezolid produced reversible myelosuppression in rats and dogs.

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. 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 C₁₆H₂₀FN₃O₄. 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. The Excipients used are Lactose Monohydrate, Starch, Sodium Starch Glycolate, 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 strip of 10 tablets each.

8.4 Storage and Handling Instructions

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

9. PATIENT COUNSELLING INFORMATION

LINOX 600 mg film-coated tablets Linezolid

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist.

- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Torglip is and what it is used for
2. What you need to know before you use Torglip
3. How to use Torglip
4. Possible side effects
5. How to store Torglip
6. Contents of the pack and other information

9.1 What LINOX 600 is and what it is used for

LINOX 600 contains Linezolid is an antibiotic of the oxazolidinone group that works by stopping the growth of certain bacteria (germs) that cause infections. It is used to treat pneumonia and some infections in the skin or under the skin. Your doctor will have decided if LINOX 600 is suitable to treat your infection.

9.2 What you need to know before you take LINOX 600

Do not take LINOX 600:

If you are allergic to LINOX 600 or any of the other ingredients of this medicine. If you are taking or have taken within the last 2 weeks any medicines known as monoamine oxidase inhibitors (MAOIs for example phenelzine, isocarboxazid, selegiline, moclobemide). These may be used to treat depression or Parkinson's disease. • If you are breastfeeding. This is because it passes into breast milk and could affect the baby.

LINOX 600 may not be suitable for you if you answer yes to any of the following questions. In this case tell your doctor as he/she will need to check your general health and your blood pressure before and during your treatment or may decide that another treatment is better for you.

Ask your doctor if you are not sure whether these categories apply to you.

- Do you have high blood pressure?
- Have you been diagnosed with an overactive thyroid?
- Do you have a tumour of the adrenal glands (phaeochromocytoma) or carcinoid syndrome (caused by tumours of the hormone system with symptoms of diarrhoea, flushing of the skin, wheezing)?
- Do you suffer from manic depression, schizoaffective disorder, mental confusion or other mental problems?
- Are you taking any of the following medicines?
 - Decongestant cold or flu remedies containing pseudoephedrine or phenylpropanolamine
 - Medicines used to treat asthma such as salbutamol, terbutaline, fenoterol
 - Antidepressants known as tricyclics or SSRIs (selective serotonin reuptake inhibitors)

for example amitriptyline, cipramil, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine; sertraline

- Medicines used to treat migraine such as sumatriptan and zolmitriptan
- Medicines used to treat sudden, severe allergic reactions such as adrenaline (epinephrine)
- Medicines which increase your blood pressure, such as noradrenaline (norepinephrine), dopamine and dobutamine
- Medicines used to treat moderate to severe pain, such as pethidine
- Medicines used to treat anxiety disorders, such as buspirone
- An antibiotic called rifampicin

Warnings and precautions

Talk to your doctor before taking LINOX 600 if you:

- bruise and bleed easily
- are anaemic
- are prone to getting infections
- have a history of seizures
- have liver problems or kidney problems particularly if you have dialysis
- have diarrhoea

Tell your doctor immediately if during treatment you suffer from:

- Problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.
- You may develop diarrhoea while taking or after taking antibiotics, including LINOX 600. If this becomes severe or persistent or you notice that your stools contain blood or mucus, you should stop taking LINOX 600 immediately and consult your doctor. In this situation, you should not take medicines that stop or slow bowel movement.
- Recurrent nausea or vomiting, abdominal pain or over breathing

Children and adolescents

LINOX 600 is not recommended for use in children and adolescents under the age of 18.

Other medicines and LINOX 600 Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. There is a risk that LINOX 600 may sometimes interact with certain other medicines to cause side effects such as changes in blood pressure, temperature or heart rate.

Tell your doctor if you are taking or have taken within the last 2 weeks the following medicines as LINOX 600 must not be taken if you are already taking these medicines or have taken them recently. (See also Section 2 above 'Do not take LINOX 600')

- Monoamine oxidase inhibitors (MAOIs for example phenelzine, isocarboxazid, selegiline, moclobemide). These may be used to treat depression or Parkinson's disease. Also tell your doctor if you are taking the following medicines. Your doctor may still decide to give you LINOX 600, but will need to check your general health and your blood pressure before and during your treatment. In other cases, your doctor may decide that another treatment is better for you.

- Decongestant cold or flu remedies containing pseudoephedrine or phenylpropanolamine.
- Some medicines used to treat asthma such as salbutamol, terbutaline, fenoterol.
- Certain antidepressants known as tricyclics or SSRIs (selective serotonin reuptake inhibitors). There are many of these, including amitriptyline, cipramil, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, sertraline.
- Medicines used to treat migraine such as sumatriptan and zolmitriptan.
- Medicines used to treat sudden, severe allergic reactions such as adrenaline (epinephrine).
- Medicines which increase your blood pressure, such as noradrenaline (norepinephrine) dopamine and dobutamine.
- Medicines used to treat moderate to severe pain, such as pethidine.
- Medicines used to treat anxiety disorders, such as buspirone.
- Medicines that stop blood clotting, such as warfarin

LINOX 600 with food and drink

- You can take LINOX 600 either before, during or after a meal.
- Avoid eating large amounts of mature cheese, yeast extracts, or soya bean extracts e.g. soy sauce and drinking alcohol, especially draught beers and wine. This is because this medicine may react with a substance called tyramine which is naturally present in some foods to cause an increase in your blood pressure.
- If you develop a throbbing headache after eating or drinking, tell your doctor or pharmacist immediately.

Pregnancy and breast-feeding

The effect of LINOX 600 in pregnant women is not known. Therefore, it should not be taken in pregnancy unless advised by your doctor. Tell your doctor if you are pregnant, think you may be pregnant or are trying to become pregnant. You should not breastfeed when taking LINOX 600 because it passes into breast milk and could affect the baby.

Driving and using machines

LINOX 600 may make you feel dizzy or experience problems with your vision. If this happens, do not drive or operate any machinery. Remember that if you are unwell your ability to drive or operate machinery may be affected. LINOX 600 film-coated tablets contains lactose If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

9.3 How to take LINOX 600

Adults

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The usual dose is one tablet (600mg LINOX 600) twice daily (every twelve hours). Swallow the tablet whole with some water.

If you are on kidney dialysis, you should take LINOX 600 after dialysis.

A course of treatment usually lasts 10 to 14 days but can last up to 28 days. The safety and effectiveness of this medicine have not been established for treatment periods longer than

28 days. Your doctor will decide how long you should be treated.

While you are taking LINOX 600, your doctor should perform regular blood tests to monitor your blood count.

Your doctor should monitor your eyesight if you take LINOX 600 for more than 28 days.

Use in children and adolescents LINOX 600 is not normally used to treat children and adolescents (under 18 years old). If you take more LINOX 600 than you should tell your doctor or pharmacist immediately. If you forget to take LINOX 600 Take the forgotten tablet as soon as you remember. Take the next tablet 12 hours after this and continue taking your tablets every 12 hours. Do not take a double dose to make up for a forgotten dose.

If you stop taking LINOX 600

Unless your doctor instructs you to stop treatment, it is important to continue taking LINOX 600. If you stop and your original symptoms come back tell your doctor or pharmacist immediately. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine also can cause side effects, although not everyone gets them.

Tell your doctor or pharmacist immediately if you notice any of these side effects during your treatment with LINOX 600:

Skin reactions such as red sore skin and flaking (dermatitis), rash, itching, or swelling, particularly around the face and neck. This may be the sign of an allergic reaction and it may be necessary for you to stop taking LINOX 600.

- Problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.
- Severe diarrhoea containing blood and/or mucus (antibiotic associated colitis including pseudomembranous colitis), which in very rare circumstances may develop into complications that are life-threatening.
- Recurrent nausea or vomiting, abdominal pain or over breathing.
- Fits or seizures have been reported with LINOX 600. You should let your doctor know if you experience agitation, confusion, delirium, rigidity, tremor, incoordination and seizure while also taking antidepressants known as SSRI's .
- Numbness, tingling or blurred vision have been reported by patients who have been given LINOX 600 for more than 28 days. If you experience difficulties with your vision you should consult your doctor as soon as possible.
- Other side effects include: Common side-effects (likely to occur in less than 1 in 10 people):
- Fungal infections especially vaginal or oral "thrush"
- Headache
- Metallic taste in the mouth
- Diarrhoea, nausea or vomiting • Changes in some blood test results including those measuring your kidney or liver function or blood sugar levels
- Unexplained bleeding or bruising, which may be due to changes in the numbers of

certain cells in the blood which may affect blood clotting or lead to anaemia
Uncommon side- effects (likely to occur in less than 1 in 100 people):

- Inflammation of the vagina or genital area in women
- Changes in numbers of certain cells in the blood which may affect your ability to fight infection
- Difficulty in sleeping
- Dizziness, sensations such as tingling or feeling numb
- Blurred vision
- “Ringing” in the ears (tinnitus)
- Increased blood pressure, inflammation of the veins
- Indigestion, stomach pain, constipation
- Dry or sore mouth, swollen, sore, or discoloured tongue
- Skin rash
- A need to urinate more often
- Fever or chills, aches and pains
- Feeling tired or thirsty
- Inflammation of the pancreas
- Increased sweating
- Changes in proteins, salts or enzymes in the blood which measure kidney or liver function.
- Reduction in the numbers of cells in the blood which fight against infection. Rare side-effects (likely to occur in less than 1 in 1000 people):
- Changes in heart rate (e.g, increase rate)
- Transient ischaemic attacks (temporary disturbance of blood flow to the brain causing short term symptoms such as loss of vision, leg and arm weakness, slurring of speech and loss of consciousness),
- Kidney failure the following side effects have also been reported (frequency not known):
- Serotonin syndrome (symptoms include fast heart rate, confusion, abnormal sweating, hallucinations, involuntary movements chills and shivering)
- Lactic acidosis (symptoms include recurrent nausea and vomiting, abdominal pain, over breathing)
- Severe skin disorders
- Convulsions
- Superficial tooth discolouration, removable with professional dental cleaning (manual descaling)
- Alopecia (hair loss)
- Hyponatraemia (low blood sodium levels)
- Changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store LINOX 600

Keep this medicine out of the sight and reach of children. This medicinal product does not require any special storage conditions. Do not use this medicine after the expiry date which is stated on the carton, blister and bottle after “EXP”. The expiry date refers to the last day of that month. For bottles: Use within 100 days after first opening. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

9.6 Contents of the pack and other information.

What LINOX 600 film-coated tablets contains

The active substance is Linezolid.

The other ingredients are Lactose Monohydrate, Starch, Sodium Starch Glycollate, Povidone K-30, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Isopropyl Alcohol, Methylene Chloride, HPMC 2910/Hypromellose, Macrogl/Peg & Titanium Dioxide.’

What LINOX 600 looks like and contents of the pack

LINOX 600 Tablets are white, capsule shaped, biconvex, film coated tablets with score on one side and plain on other side.

LINOX 600 is available in blister strip of 10 tablets each.’

10. DETAILS OF MANUFACTURER

Manufactured by:

TORRENT PHARMACEUTICALS LTD

32 No. Middle Camp, NH-10,

East district, Gangtok, Sikkim-737135.

OR

Uni Medicolabs

25 & 26, Pharmacity, Selaqui,

Dehradun, Uttarakhand.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

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

OR

Mfg Licence No.: 29/UA/2018 issued on 19.11.2020

12. DATE OF REVISION

sep-2022

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/ LINOX 600 mg/sep 2022 /02/PI