BACTOLID
(Linezolid Film-Coated Tablets 600mg)
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1. NAME OF THE MEDICINAL PRODUCT

BACTOLID (Linezolid Film-Coated Tablets 600mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600mg of linezolid.

Excipients with known effect:
Each tablet contains 139.600 mg of Lactose monohydrate.
Linezolid film-coated tablets 600 mg contains less than 1 mmol sodium (23mg) per film-coated tablet, that is to say essentially 'sodium-free'.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

3.1 Product description

White to off white, oval shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side and 'L8' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Linezolid formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms. Linezolid is active against Gram-positive bacteria only. Linezolid has no clinical activity against Gram-negative pathogens. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected.

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

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and - resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

Complicated skin and skin structure infections including diabetic foot infections, without concomitant osteomyelitis caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Linezolid has not been studied in the treatment of decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*.

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).
Due to concerns about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with linezolid in the outpatient setting.
Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to linezolid. Therapy may be instituted empirically while awaiting the results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

4.2 Posology and method of administration

Patients whose therapy is started with linezolid injection may be switched to linezolid tablets, with no dosage adjustment.

Table 1. Dosage Guidelines for Linezolid

Infection*	Dosage and Route of Administration: Pediatric Patients† (Birth through 11 Years of Age)	Dosage and Route of Administration: Adults and Adolescents (12 Years and Older)	Recommended Duration of Treatment (consecutive days)
Complicated skin and skin structure infections	10 mg/kg oral‡ q8h	600 mg oral‡ q12h	10 to 14
Community- acquired pneumonia, including concurrent bacteremia			
Nosocomial pneumonia			
Vancomycin resistant *Enterococcus faecium* infections, including concurrent bacteremia	10 mg/kg oral‡ q8h	600 mg oral‡ q12h	14 to 28
Uncomplicated skin and skin structure infections	< 5 yrs: 10 mg/kg oral‡ q8h 5-11 yrs: 10 mg/kg oral‡ q12h	Adults: 400 mg oral‡ q12h Adolescents: 600 mg oral ‡ q12h	10 to 14

* Due to the designated pathogens.
† **Neonates < 7 days:** Most pre-term neonates < 7days of age (gestational age < 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life.
‡ Oral dosing using Linezolid Tablets.

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 hemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by hemodialysis, but the concentrations of these metabolites are still very considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

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

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

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.

4.3 Contraindications

Linezolid is contraindicated in patients who have previously demonstrated hypersensitivity to linezolid or any of the other product components.

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

Potential Interactions Producing Elevation of Blood Pressure
Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine, phenylpropanolamine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine).

Potential Serotonergic Interactions
Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine or buspirone.

4.4 Special warning and precautions for use

Reversible myelosuppression (anemia, thrombocytopenia, leukopenia, and pancytopenia) that may be dependent on duration of therapy has been reported in some patients receiving linezolid. Thrombocytopenia may occur more often in patients with severe renal insufficiency, whether or not on dialysis, and in patients with moderate to severe hepatic impairment. Monitoring of complete blood counts should be considered for patients who are at increased risk for bleeding, who have pre-existing myelosuppression, who have severe renal insufficiency or moderate to severe hepatic impairment, who receive concomitant medications that may decrease hemoglobin levels or platelet count or function, or who receive linezolid for more than 2 weeks.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid, and may range in severity from mild to life-threatening.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including linezolid, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C.difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Peripheral and optic neuropathy have been reported in patients treated with linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration.

If symptoms of visual impairment appear, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. Visual function should be monitored in all patients taking linezolid for extended periods (greater than or equal to 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with linezolid. If peripheral or optic neuropathy occurs, the continued use of linezolid in these patients should be weighed against the potential risks.

Lactic acidosis has been reported with the use of linezolid. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical attention.

Convulsions have been reported to occur rarely in patients when treated with linezolid. In most of these cases, a history of seizures or risk factors for seizures were reported.

Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and opioids have been reported.

Where administration of linezolid and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed.

Rhabdomyolysis has been reported with the use of linezolid. If signs or symptoms of rhabdomyolysis are observed, linezolid should be discontinued and appropriate therapy initiated.

Hyponatremia and/or Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) have been observed in some patients treated with linezolid. It is recommended that serum sodium levels be monitored regularly in the elderly, in patients taking diuretics, and in other patients at risk of hyponatremia.

In healthy volunteers, co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid C_{max} and a 32% decrease in linezolid AUC. The clinical significance of this interaction is unknown.

Linezolid has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected. Linezolid should be used with special caution in patients at high risk for life threatening systemic infections, such as those with infections related to central venous catheters in intensive care units. Linezolid is not approved for the treatment of patients with catheter related bloodstream infections.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Linezolid is a weak, reversible, nonselective inhibitor of monoamine oxidase. Therefore, some patients receiving linezolid may experience a mild reversible enhancement on the pressor response induced by pseudoephedrine HCl or phenylpropanolamine HCl. Initial doses of adrenergic agents, such as dopamine or dopamine agonists, should be reduced and titrated to achieve the desired response.

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

Antibiotics: The pharmacokinetics of linezolid were not altered when administered together with either aztreonam or gentamicin. The effect of rifampin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampin 600 mg once daily for 8 days. Rifampin decreased the linezolid 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.

4.6 Fertility, pregnancy and lactation

Reproductive studies performed in mice and rats treated with linezolid showed no evidence of teratogenic effects. Mild fetal toxicity was observed in mice only at maternally toxic dose levels. In rats, fetal toxicity was manifested as decreased fetal body weights and reduced ossification of sternebrae (which is often seen in association with decreased body weights). Reduced pup survival and mild maturational delays occurred in rats. When mated, these same pups showed evidence of a reversible, dose related increase in pre-implantation loss. There are no adequate and well-controlled studies in pregnant women. Therefore, linezolid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Linezolid decreased the fertility of male rats.

Linezolid transferred into the breast milk of lactating laboratory rats. It is not known whether linezolid is excreted in human milk. Therefore, caution should be exercised when linezolid is administered to a nursing woman.

4.7 Effect on ability to drive and use machines

The effect of linezolid on the ability to drive or operate machinery has not been systematically evaluated.

4.8 Side effects

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.3

Dimensions: 200X 300mm
BLACK

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Frequency Not Known (cannot be estimated from the available data)
Infections and infestations	Moniliasis			
Blood and lymphatic system disorders	Thrombocytopenia*, Anemia*	Pancytopenia*, Leucopenia*.	Sideroblastic anemia*	
Immune system disorders			Anaphylaxis*	
Metabolism and nutrition disorders			Lactic acidosis*	
Nervous system disorders	Headache	Convulsions*, Peripheral neuropathy*, Taste alteration,		
Eye disorders		Optic neuropathy*		
Gastrointestinal disorders	Vomiting, Diarrhea, Nausea, Abdominal pain including abdominal cramps	Abdominal cramps#, Abdominal distension, Tongue discoloration*	Superficial tooth discoloration*	
Skin and subcutaneous tissue disorders	Rash*	Bullous skin disorders, Severe cutaneous adverse reactions, Angioedema*	Toxic epidermal necrolysis* §, Stevens Johnson syndrome* §, Hypersensitivity vasculitis*	
Musculoskeletal and connective tissue disorders			Rhabdomyolysis*	
Investigations	Abnormal liver function tests	Abnormal hematology tests		

*ADR identified post-marketing
§ ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3".
# The ADR Abdominal cramps is defined by MedDRA LLT and not by PT.

4.9 Symptoms and treatment of overdose

In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis removes approximately 30% of a dose of linezolid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J01XX08

General Properties

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

Susceptibility

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

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.

5.2 Pharmacokinetic properties

Absorption

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

Plasma linezolid 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.

Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended.

Metabolism

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

Elimination

In patients with normal renal function or mild to moderate renal insufficiency, linezolid is primarily excreted under steady-state conditions in the urine as PNU-142586 (40%), parent drug (30%) and PNU-142300 (10%). Virtually no parent drug is found in the feces while approximately 6% and 3% of each dose appears as PNU-142586 and PNU142300, 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 < 30mL/min). However, there was no increase in AUC of parent drug. Although there is some removal of the major metabolites of linezolid by hemodialysis, metabolite plasma levels after single 600 mg doses were still considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

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

The clinical significance of these observations has not been established as limited safety data are currently available.

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

Children and adolescents (< 18 years old): In adolescents (12 to 17 years old), linezolid pharmacokinetics were similar to that in adults following a 600 mg dose. Therefore, adolescents administered 600 mg every 12 hours daily will have similar exposure to that observed in adults receiving the same dosage.

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

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

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

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

6. PHARMACEUTICALS PARTICULARS

6.1 List of excipients

Tablet core: Lactose monohydrate, Maize starch, Hydroxypropyl cellulose, Sodium starch glycolate, Magnesium stearate, Purified water.

Film-coating (Opadry White 03B58895): Hypromellose (E464), Titanium dioxide (E171), Macrogol (E1521), Carnauba wax.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Storage condition

Store below 30ºC. Protect from light and moisture.

6.5 Packaging available

3 x 10's Alu-Alu Blister pack

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF MANUFACTURER

HETERO LABS LIMITED
Unit V Block-V and Block-VA,
TSIIC Formulation SEZ
S. Nos. 439 440 441 and 458,
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8. PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION

30 March 2026