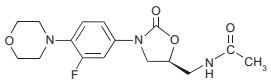
Zoldap™

[L i n e z o l i d]

زولڈیپ

400mg & 600mg Tablets

DESCRIPTION
Zoldap Tablets contain Linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for Linezolid is *N*-[[(*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5 -oxazolidinyl]methyl]acetamide. Its molecular formula is $C_{16}H_{20}FN_3O_4$ and the structural formula is:



Linezolid

QUALITATIVE AND QUANTITATIVE COMPOSITION
Zoldap (Linezolid) Tablets are available for oral administration as:

Zoldap Tablets 400mg
Each film-coated tablet contains:
Linezolid USP...400mg

Zoldap Tablets 600mg
Each film-coated tablet contains:
Linezolid USP...600mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Linezolid is a synthetic, antibacterial agent belonging to the class of antibiotics, the oxazolidinones, with *in-vitro* activity against Gram-positive aerobic bacteria, some Gram-positive anaerobic bacteria and certain Gram-negative bacteria. It selectively inhibits bacterial protein synthesis via a mechanism of action different from that of other antibacterial agents. Linezolid binds to the 23S ribosomal RNA of the 50S subunit of the bacterial ribosome and prevents the formation of a functional 70S initiation complex which is an essential component of the bacterial translation process. The time-kill studies have shown Linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, Linezolid was found to be bactericidal for the majority of strains.

Microbiology
Linezolid has been shown to be active against most isolates of the following microorganism, both *in-vitro* and in clinical infections:

<u>*Gram positive aerobes*</u>
Enterococcus faecalis
Enterococcus faecium
Staphylococcus aureus
Coagulase negative staphylococci
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Group C streptococci
Group G streptococci

<u>*Gram positive anaerobes*</u>
Clostridium perfringens
Peptostreptococcus anaerobius
Peptostreptococcus species

<u>*Gram-negative aerobes*</u>
Pasteurella canis
Pasteurella multocida

<u>*Resistant organisms*</u>
Haemophilus influenzae
Moraxella catarrhalis
Neisseria species
Enterobacteriaceae
Pseudomonas aeruginosa

Mechanisms of Resistance
Resistance to Linezolid is associated with point mutations in the 23S rRNA. The Linezolid resistance in these organisms is associated with a point mutation in the 23S rRNA (substitution of thymine for guanine at position 2576) of the organism. Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to Linezolid.
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.

Pharmacokinetics
Absorption
Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing and the absolute bioavailability is approximately 100%. Steady-state conditions are achieved by the second or third day of dosing.
<u>Effect of food</u>
Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with Linezolid. However, the total exposure measured as $AUC_{0-\infty}$ values is similar under both conditions.

Distribution
Linezolid is readily distributed to well perfused tissues. Its 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.

Metabolism
Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid metabolite (A) and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a non-enzymatic chemical oxidation mechanism *in-vitro*. *In-vitro* studies have demonstrated that Linezolid is minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of Linezolid is not fully understood.

Elimination
Nonrenal clearance accounts for approximately 65% of the total clearance of Linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as Linezolid, 40% as metabolite B and 10% as metabolite A. The mean renal clearance of Linezolid is 40 mL/min which suggests net tubular reabsorption. Virtually no Linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B and 3% as metabolite A.
A small degree of nonlinearity in clearance was observed with increasing doses of Linezolid, which appears to be due to lower renal and nonrenal clearance of Linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

Special Population
Renal impairment
Because similar plasma concentrations of Linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal impairment. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of Linezolid in patients with renal impairment should be weighed against the potential risks of accumulation of these metabolites. After single doses of 600mg, 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.

Hepatic impairment
The pharmacokinetics of Linezolid are not altered in patients with mild to moderate hepatic insufficiency (i.e., Child-Pugh class A or B). Dose adjustment in such patients is not required. 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.

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

THERAPEUTIC INDICATIONS
Zoldap (Linezolid) is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Zoldap (Linezolid) is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

Pneumonia
- Nosocomial pneumonia caused by Staphylococcus aureus (methicillin-susceptible and -resistant isolates) or Streptococcus pneumoniae.
- Community-acquired pneumonia caused by Streptococcus pneumoniae, including cases with concurrent bacteremia or Staphylococcus aureus (methicillin-susceptible isolates).

Skin and Skin Structure Infections
- Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis caused by Staphylococcus aureus (methicillin-susceptible and -resistant isolates), Streptococcus pyogenes or Streptococcus agalactiae.
- Uncomplicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible isolates only) or Streptococcus pyogenes.

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

DOSAGE & ADMINISTRATION
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zoldap (Linezolid) and other antibacterial drugs, Zoldap (Linezolid) should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.
The recommended dosage for Zoldap (Linezolid) for the treatment of infection is described in Table below. 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.

Dosage Guidelines for Linezolid

Infection	Dosage, Route and Frequency of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric patients† (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Nosocomial pneumonia	10mg/kg intravenously or oral every 8 hours	600mg intravenously or oral every 12 hours	10 to 14
Community-acquired pneumonia, including concurrent bacteremia			
Complicated skin and skin structure infections			
Vancomycin-resistant Enterococcus faecium infections, including concurrent bacteremia	10mg/kg intravenously or oral every 8 hours	600mg intravenously or oral every 12 hours	14 to 28
Uncomplicated skin and skin structure infections	Less than 5 yrs:10mg/kg oral every 8 hours 5 -11 yrs: 10mg/kg oral every 12 hours	Adults: 400mg oral every 12 hours Adolescents: 600mg oral every 12 hours	10 to 14

†Neonates less than 7 days: Most pre-term neonates less than 7 days of age (gestational age less than 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 every 12 hours. Consideration may be given to the use of 10 mg/kg every 8 hours regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg every 8 hours by 7 days of life.

Special Population
Elderly
No dose adjustment is required.

Renal impairment
No dose adjustment is required. However, Zoldap (Linezolid) should be used with special caution in patients with severe renal insufficiency and in patients with severe renal insufficiency who are undergoing dialysis and only when the anticipated benefit is considered to outweigh the theoretical risk.

Hepatic impairment
No dose adjustment is required. However, it is recommended that Zoldap (Linezolid) should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk.

ADVERSE REACTIONS
Common:
Diarrhoea, nausea, vomiting, headache, candidiasis, oral candidiasis, vaginal candidiasis, fungal infections, anaemia, insomnia, taste perversion (metallic taste), dizziness, hypertension, localized or general abdominal pain, constipation, dyspepsia, abnormal liver function test, increased AST, ALT or alkaline phosphatase, increased BUN, increased LDH, creatine kinase, lipase, amylase or non fasting glucose, decreased total protein, albumin, sodium or calcium, increased or decreased potassium or bicarbonate, pruritus, rash, fever, localized pain, increased neutrophils or eosinophils, decreased haemoglobin, haematocrit or red blood cell count and increased or decreased platelet or white blood cell counts.

Uncommon:
Vaginitis, leucopenia, neutropenia, thrombocytopenia, eosinophilia, hyponatraemia, convulsions, hypoaesthesia, paraesthesia, blurred vision, tinnitus, arrhythmia (tachycardia), transient ischaemic attacks, phlebitis, thrombophlebitis, pancreatitis, gastritis, abdominal distention, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder increased total bilirubin, urticaria, dermatitis, diaphoresis, renal failure, increased creatinine, polyuria, vulvovaginal disorder, chills, fatigue, increased thirst, increased sodium or calcium, decreased non fasting glucose, increased or decreased chloride and increased reticulocyte count.

Rare:
Antibiotic-associated colitis, including pseudomembranous colitis, pancytopenia, changes in visual field defect and superficial tooth discolouration.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Linezolid is contraindicated in patients:
- Who have known hypersensitivity to Linezolid or to any of the excipient of the product.
- 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.

PRECAUTIONS
Myelosuppression
Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving Linezolid. In cases where the outcome is known, when Linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive Linezolid, particularly in those who receive Linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with Linezolid should be considered in patients who develop or have worsening myelosuppression.

Peripheral and Optic Neuropathy
Peripheral and optic neuropathies have been reported in patients treated with Linezolid, primarily in those patients treated for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision or visual field defect, prompt ophthalmic evaluation is recommended. If peripheral or optic neuropathy occurs, the continued use of Linezolid in these patients should be weighed against the potential risks.

Serotonin Syndrome
Spontaneous reports of serotonin syndrome including fatal cases associated with the co-administration of Linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Unless clinically appropriate and patients are carefully observed for signs and/or symptoms of serotonin syndrome or neuroleptic malignant syndrome-like (NMS-like) reactions, 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, bupropion or buspirone.

Clostridium difficile Associated Diarrhea
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. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile and surgical evaluation should be instituted as clinically indicated.

Mortality imbalance in patients with catheter-related Gram positive bloodstream infections
Linezolid should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

Lactic Acidosis
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 evaluation.

Convulsions
Convulsions have been reported in patients when treated with Linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported.

Hypoglycemia
Postmarketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with Linezolid. Diabetic patients should be cautioned of potential hypoglycemic reactions when treated with Linezolid. If hypoglycemia occurs, a decrease in the dose of insulin or oral hypoglycemic agent or discontinuation of oral hypoglycemic agent, insulin or Linezolid may be required.

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

Superinfection
The effects of Linezolid therapy on normal flora have not been evaluated. The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

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.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Linezolid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether Linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Linezolid is administered to a nursing woman.

DRUG INTERACTIONS
Adrenergic Agents
Patients receiving Linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content Information. It is recommended that doses of adrenergic agents, vasopressor or dopaminergic agents, should be carefully titrated to achieve the desired response when co-administered with Linezolid.

Serotonergic Agents
Spontaneous reports of serotonin syndrome associated with co-administration of Linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with Linezolid and concomitant serotonergic agents should be closely observed for signs and symptoms of serotonin syndrome (e.g., cognitive dysfunction, hyperpyrexia, hyperreflexia, incoordination). If any signs or symptoms occur, consider discontinuation of either one or both agents (Linezolid or concomitant serotonergic agents). If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed.

Warfarin
When warfarin was added to Linezolid therapy at steady-state, there was a 10% reduction in mean maximum international normalized ratio (INR) on coadministration with a 5% reduction in AUC INR.

OVERDOSAGE:
No specific antidote is known. No cases of overdose have been reported. However, in case of overdose 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.

STORAGE
Do not store above 30°C.
Protect from light and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Zoldap (Linezolid) Tablets 400mg are available in blister pack of 10's.
Zoldap (Linezolid) Tablets 600mg are available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
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