140mm

210mm

Xolid
(Linezolid)

Tablet
Suspension
Infusion

زولڈ
(لنزولڈ)
ٹیبلٹ
سسپنشن
انفیوژن

COMPOSITION
Xolid Tablet 600mg
Each film coated tablet contains:
Linezolid.....600mg
(USP Specifications)
Xolid Dry Suspension 100mg/5ml
Each 5ml (after reconstitution) contains:
Linezolid.....100mg
(Innovator's Specification)
Xolid Infusion 200mg/100ml
Each 100ml solution for infusion contains:
Linezolid.....200mg
(Innovator's Specification)
Xolid Infusion 400mg/200ml
Each 200ml solution for infusion contains:
Linezolid.....400mg
(Innovator's Specification)
Xolid Infusion 600mg/300ml
Each 300ml solution for infusion contains:
Linezolid.....600mg
(Innovator's Specification)

DESCRIPTION
XOLID for oral suspension contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class.

MECHANISM OF ACTION
Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones, which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The in vitro spectrum of activity of linezolid also includes certain Gram-negative bacteria and anaerobic bacteria. Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of isolates.

INDICATIONS
XOLID is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. XOLID 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 only).
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*. XOLID has not been studied in the treatment of decubitus ulcers.
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 AND ADMINISTRATION
The recommended dosage for XOLID formulations for the treatment of infections is described below:
Reconstitution of Oral Suspension
To make 60ml suspension add 20ml freshly boiled and cooled water into the bottle with the help of measuring cup provided in the pack. Invert and shake to wet the powder in the bottle. Then add further 20ml water and invert to make suspension.
Intravenous Administration
XOLID I.V. Infusion is supplied in single-use, ready-to-use infusion bottle. Parenteral drug products should be inspected visually for particulate matter prior to administration.
XOLID I.V. Infusion should be administered by intravenous infusion over a period of 30 to 120 minutes. **Do not use this intravenous infusion in series connections**.
Additives should not be introduced into this solution. If XOLID I.V. Infusion is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product. In particular, physical incompatibilities resulted when XOLID I.V. Infusion was combined with the following drugs during simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isothionate, erythromycin lactobionate, phenytoin sodium, and trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when XOLID I.V. Infusion was combined with ceftriaxone sodium.
If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of XOLID I.V. Infusion with an infusion solution compatible with XOLID I.V. Infusion and with any other drug(s) administered via this common line.

PHARMACOKINETICS
Absorption: Linezolid is extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, linezolid may be given orally or intravenously without dose adjustment.
Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as $AUC_{0-\infty}$ is similar under both conditions.
Distribution: Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well-perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent. The volume of distribution of linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers.
Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase 1 volunteer studies following multiple dosing of linezolid. The ratio of linezolid in saliva relative to plasma was 1.2 to 1 and the ratio of linezolid in sweat relative to plasma was 0.55 to 1.
Metabolism: Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the 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

Dosage and Route of Administration

Infection	Pediatric Patients (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	Recommended Duration of Treatment (consecutive days)
Nosocomial pneumonia	10 mg/kg oral/IV every 8 hours	600 mg oral/IV 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	10 mg/kg oral/IV every 8 hours	600 mg oral/IV every 12 hours	14 to 28
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral every 8 hours. 5-11 yrs: 10 mg/kg oral every 12 hours	Adults: 400 mg oral every 12 hours. Adolescents: 600 mg oral every 12 hours	10 to 14

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

Excretion: Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as linezolid, 40% as metabolite B, and 10% as metabolite A. The mean renal clearance of linezolid is 40 mL/min which suggests net tubular reabsorption. Virtually no linezolid appears in the 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 non-renal clearance of linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

WARNINGS AND 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 XOLID, primarily in 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. Visual blurring has been reported in some patients treated with XOLID for less than 28 days. Peripheral and optic neuropathy has also been reported in children.

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. Visual function should be monitored in all patients taking XOLID for extended periods (≥ 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with XOLID. If peripheral or optic neuropathy occurs, the continued use of XOLID 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 XOLID 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.

In some cases, a patient already receiving a serotonergic antidepressant or buspirone may require urgent treatment with linezolid. If alternatives to linezolid are not available and the potential benefits of linezolid outweigh the risks of serotonin syndrome or NMS-like reactions, the serotonergic antidepressant should be stopped promptly and linezolid administered. The patient should be monitored for two weeks (five weeks if fluoxetine was taken) or until 24 hours after the last dose of linezolid, whichever comes first. Symptoms of serotonin syndrome or NMS-like reactions include hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that include extreme agitation progressing to delirium and coma. The patient should also be monitored for discontinuation symptoms of the antidepressant (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).

Mortality Imbalance in an Investigational Study in Patients with Catheter-Related Bloodstream Infections, including those with catheter-site infections: An imbalance in 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%); odds ratio 1.426, 95% CI 0.970, 2.098]. While causality has not been established, this observed imbalance occurred primarily in linezolid-treated patients in whom either Gram-negative pathogens, mixed Gram negative and Gram-positive pathogens, or no pathogen were identified at baseline, but was not seen in patients with Gram-positive infections only.

Linezolid is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. Linezolid has no clinical activity against Gram-negative pathogens and 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.

***Clostridium difficile* Associated Diarrhea:** *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XOLID, 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.

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.

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

Lactic Acidosis: Lactic acidosis has been reported with the use of XOLID. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving XOLID 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: Post-marketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid, a reversible, nonselective MAO inhibitor. Some MAO inhibitors have been associated with hypoglycemic episodes in diabetic patients receiving insulin or hypoglycemic agents. While a causal relationship between linezolid and hypoglycemia has not been established, 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 XOLID 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.

SIDE EFFECTS

The following adverse reactions have been identified during post approval use of XOLID.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during post-marketing use of XOLID.

Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with XOLID.

Lactic acidosis has been reported with the use of XOLID. Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy.

Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and XOLID.

Convulsions have been reported with the use of XOLID.

Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens-Johnson syndrome have been reported.

Superficial tooth discoloration and tongue discoloration have been reported with the use of linezolid. The tooth discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome.

Hypoglycemia, including symptomatic episodes, has also been reported.

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase.

Adrenergic and Serotonergic Agents: Linezolid has the potential for interaction with adrenergic and serotonergic agents.

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

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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy: Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.06-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen. There are no adequate and well-controlled studies in pregnant women. XOLID 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 XOLID is administered to a nursing woman.

OVERDOSE

In the event of over dosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

CONTRAINDICATIONS

XOLID is contraindicated for use in patients who have known 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.

STORAGE & INSTRUCTIONS

Store between 15-25°C.
Protect from heat, sunlight and moisture.
Keep away from the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Injection may exhibit a change in color that can intensify with the passage of time without adversely affecting the potency.

HOW SUPPLIED

Xolid Tablet 600mg 12 Tablets
Xolid Dry Suspension 100mg/5ml 60 ml.
Xolid Infusion 200mg/100ml 1 Vial
Xolid Infusion 400mg/200ml 1 Vial
Xolid Infusion 600mg/300ml 1 Vial

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔ دھوپ، گرمی، نمی سے محفوظ اور بچوں کی پہنچ سے دور رکھیں۔ صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:

PHARMASOL
PRIVATE LIMITED

Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.