

# Averozolid

**Linezolid 200 mg/100ml**

**solution in vial for I.V. Infusion**

## **INDICATIONS AND USAGE**

Averozolid is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Averozolid 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 [see Warnings and Precautions].

### 1- 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).

### 2- 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*. Averozolid 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*.

### 3- Vancomycin-resistant Enterococcus faecium Infections

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

### 4- Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Averozolid and other antibacterial drugs, Averozolid should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. The safety and efficacy of Averozolid formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

## **DOSAGE AND ADMINISTRATION**

## General Dosage and Administration

The recommended dosage for Averozolid formulations for the treatment of infections is described in Table 1.

Table 1. Dosage Guidelines for Averozolid

Infection*	Dosage, Route and Frequency of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients <sup>†</sup> (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Nosocomial pneumonia Community acquired pneumonia, including concurrent bacteremia Complicated skin and skin structure infections	10 mg/kg intravenously every 8 hours	600 mg intravenously every 12 hours	10 to 14
Vancomycin resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg intravenously every 8 hours	600 mg intravenously every 12 hours	14 to 28

\* Due to the designated pathogens [see Indications and Usage]

<sup>†</sup> 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 [see Use in Specific Populations and Clinical Pharmacology].

### Intravenous Administration

Averozolid I.V. Injection is supplied in single-use, ready-to-use infusion bags. Parenteral drug products should be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bag. If leaks are detected, discard the solution, as sterility may be impaired. Keep the infusion bags in the overwrap until ready to use. Each overwrap contains a peel-off label. Store at temperature not exceeding 30 ° C. to be used immediately after opening. Protect from freezing.

*Averozolid I.V. Injection may exhibit a yellow color that can intensify over time without adversely affecting potency.*

Averozolid I.V. Injection should be administered by intravenous infusion over a period of 30 to 120 minutes. Do not use this intravenous infusion bag in series connections. Additives should not be introduced into this solution. If Averozolid I.V. Injection 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.

If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of Averozolid I.V. Injection with an infusion solution compatible with Averozolid I.V. Injection and with any other drug(s) administered via this common line.

### Compatibilities

Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP.

### Incompatibilities

Physical incompatibilities resulted when Averozolid I.V. Injection 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 Averozolid I.V. Injection was combined with ceftriaxone sodium.

## **CONTRAINDICATIONS**

### 1- Hypersensitivity

Averozolid formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

### 2- 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.

## **WARNINGS AND PRECAUTIONS**

### 1- 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.

### 2- Peripheral and Optic Neuropathy

Peripheral and optic neuropathies have been reported in patients treated with Averozolid, 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 Averozolid 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 Averozolid for extended periods ( $\geq 3$  months) and in all patients reporting new visual symptoms regardless of length of therapy with Averozolid. If peripheral or optic neuropathy occurs, the continued use of Averozolid in these patients should be weighed against the potential risks.

### 3- Serotonin Syndrome

Spontaneous reports of serotonin syndrome including fatal cases associated with the co-administration of Averozolid 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 reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT<sub>1</sub> receptor agonists (triptans), meperidine, bupropion, or buspirone [see Drug Interactions and Clinical Pharmacology].

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).

### 4- 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 [see Indications and Usage].

## 5- *Clostridium difficile* Associated Diarrhea

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

## 6- 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) [see Drug Interactions and Clinical Pharmacology].

## 7- Lactic Acidosis

Lactic acidosis has been reported with the use of Averozolid. 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 Averozolid should receive immediate medical evaluation.

## 8- 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.

## 9- Hypoglycemia

Postmarketing 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.

## 10- Development of Drug-Resistant Bacteria

Prescribing Averozolid 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.

## **ADVERSE REACTIONS**

### **Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### **Treatment–Emergent Adverse Reactions Occurring in >1% of Adult Patients Treated with Averozolid in Comparator-Controlled Clinical Trials**

Headache –Diarrhea -Nausea –Vomiting –Dizziness –Rash – Anemia –Taste alteration- Vaginal moniliasis - Oral moniliasis - Abnormal liver function tests- Fungal infection - Tongue discoloration - Localized abdominal pain - Generalized abdominal pain

#### **Treatment-Emergent Adverse Reactions Occurring in > 1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-Controlled Clinical Trials**

Diarrhea- Vomiting- Headache- Anemia- Thrombocytopenia- Nausea- Generalized abdominal pain- Localized abdominal pain- Loose stools- Eosinophilia- Pruritus at non-application site- Vertigo.

### **Laboratory Abnormalities:**

Linezolid has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. Thrombocytopenia associated with the use of Linezolid appears to be dependent on duration of therapy (generally greater than 2 weeks of treatment) the platelet counts for most patients returned to the normal range/baseline during the follow-up period. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for Linezolid; the role of linezolid in these events cannot be determined [see Warning and Precautions]

### **Postmarketing Experience**

The following adverse reactions have been identified during post approval use of Averozolid. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) [see Warnings and Precautions]; sideroblastic anemia.

Peripheral neuropathy and optic neuropathy sometimes progressing to loss of vision [see Warnings and Precautions].

Lactic acidosis [see Warnings and Precautions]. 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 Averozolid [see Warnings and Precautions].

Convulsions [see Warnings and Precautions].

Anaphylaxis, angioedema, and bullous skin disorders including severe cutaneous adverse reactions (SCAR) such as toxic epidermal necrolysis and Stevens-Johnson syndrome.

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 [see Warnings and Precautions].

## **DRUG INTERACTIONS**

### **1- Monoamine Oxidase Inhibitors**

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. [See Contraindications and Clinical Pharmacology].

### **2- Adrenergic and Serotonergic Agents**

Linezolid has the potential for interaction with adrenergic and serotonergic agents. [See Warnings and Precautions and Clinical Pharmacology].

## **USE IN SPECIFIC POPULATIONS**

### **Pregnancy**

Teratogenic Effects – Pregnancy Category C

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 (see Non-teratogenic Effects). There are no adequate and well-controlled studies in pregnant women. Averozolid 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 Averozolid is administered to a nursing woman.

## **Pediatric Use**

The safety and effectiveness of Averozolid for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years [see Indications and Usage, Clinical Pharmacology]:

- Nosocomial pneumonia
- Complicated skin and skin structure infections
- Community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years)
- vancomycin-resistant *Enterococcus faecium* infections

The safety and effectiveness of Averozolid for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years:

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

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.

The pharmacokinetics of linezolid has been evaluated in pediatric patients from birth to 17 years of age. In general, weight-based clearance of linezolid gradually decreases with increasing age of pediatric patients. However, in preterm (gestational age < 34 weeks) neonates < 7 days of age, linezolid clearance is often lower than in full-term neonates < 7 days of age. Consequently, preterm neonates < 7 days of age may need an alternative linezolid dosing regimen of 10 mg/kg every 12 hours [see Dosage and Administration and Clinical Pharmacology].

## **Geriatric Use**

No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

## **OVERDOSAGE**

In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Averozolid is an antibacterial drug [see Microbiology].

### Pharmacodynamics

In a randomized, positive- and placebo-controlled crossover thorough QT study, 40 healthy subjects were administered a single Averozolid 600 mg dose via a 1 hour IV infusion, a single Averozolid 1200 mg dose via a 1 hour IV infusion, placebo. At both the 600 mg and 1200 mg Averozolid doses, no significant effect on QTc interval was detected at peak plasma concentration or at any other time.

### Pharmacokinetics

The mean pharmacokinetic parameters of linezolid in adults after single and multiple intravenous doses are summarized in Table 2.

Table 2. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	C <sub>max</sub> mcg/mL	C <sub>min</sub> mcg/mL	T <sub>max</sub> hrs	AUC* mcg•h/mL	t <sub>1/2</sub> hrs	CL mL/min
600 mg IV injection ‡ single dose	12.90 (1.60)	---	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
every 12 hours	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)

\* AUC for single dose = AUC<sub>0-∞</sub>; for multiple dose = AUC<sub>0-τ</sub>

‡ Data dose-normalized from 625 mg, intravenous dose was given as 0.5-hour infusion.

C<sub>max</sub> = Maximum plasma concentration; C<sub>min</sub> = Minimum plasma concentration; T<sub>max</sub> = Time to C<sub>max</sub>; AUC = Area under concentration-time curve; t<sub>1/2</sub> = Elimination half-life; CL = Systemic clearance

### 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<sub>max</sub> is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as AUC<sub>0-∞</sub> 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 minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of linezolid is not fully understood.

## Excretion

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.

## Specific Populations

### Geriatric Patients

The pharmacokinetics of linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

### Pediatric Patients

The pharmacokinetics of linezolid following a single intravenous dose were investigated in pediatric patients ranging in age from birth through 17 years (including premature and full-term neonates), in healthy adolescent subjects ranging in age from 12 through 17 years, and in pediatric patients ranging in age from 1 week through 12 years. The pharmacokinetic parameters of linezolid are summarized in Table 3 for the pediatric populations studied and healthy adult subjects after administration of single intravenous doses.

The  $C_{max}$  and the volume of distribution ( $V_{ss}$ ) of linezolid are similar regardless of age in pediatric patients. However, plasma clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, weight-based clearance is most rapid in the youngest age groups ranging from < 1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and a shorter half-life as

compared with adults. As the age of pediatric patients increases, the weight-based clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population. There is increased inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours relative to adolescents or adults dosed every 12 hours. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg every 8 hours. Pediatric patients 12 years and older should receive 600 mg every 12 hours [see Dosage and Administration].

Table 3. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg Linezolid (Mean: (%CV); [Min, Max Values])

Age Group	C <sub>max</sub> mcg/mL	V <sub>ss</sub> L/kg	AUC* mcg·h/mL	t <sub>1/2</sub> hrs	CL mL/min/kg
Neonatal Patients Pre-term** < 1 week (N=9)†	12.7 (30%) [9.6, 22.2]	0.81 (24%) [0.43, 1.05]	108 (47%) [41, 191]	5.6 (46%) [2.4, 9.8]	2.0 (52%) [0.9, 4.0]
Full-term*** < 1 week (N=10)† -Full-term***	11.5 (24%) [8.0, 18.3]	0.78 (20%) [0.45, 0.96]	55 (47%) [19, 103]	3.0 (55%) [1.3, 6.1]	3.8 (55%) [1.5, 8.8]
≥ 1 week to ≤ 28 days (N=10)†	12.9 (28%) [7.7, 21.6]	0.66 (29%) [0.35, 1.06]	34 (21%) [23, 50]	1.5 (17%) [1.2, 1.9]	5.1 (22%) [3.3, 7.2]
Infant Patients > 28 days to < 3 Months (N=12)†	11.0 (27%) [7.2, 18.0]	0.79 (26%) [0.42, 1.08]	33 (26%) [17, 48]	1.8 (28%) [1.2, 2.8]	5.4 (32%) [3.5, 9.9]
Pediatric Patients 3 months through 11 years† (N=59)	15.1 (30%) [6.8, 36.7]	0.69 (28%) [0.31, 1.50]	58 (54%) [19, 153]	2.9 (53%) [0.9, 8.0]	3.8 (53%) [1.0, 8.5]
Adolescent Subjects and Patients 12 through 17 years‡ (N=36)	16.7 (24%) [9.9, 28.9]	0.61 (15%) [0.44, 0.79]	95 (44%) [32, 178]	4.1 (46%) [1.3, 8.1]	2.1 (53%) [0.9, 5.2]
Adult Subjects§ (N= 29)	12.5 (21%) [8.2, 19.3]	0.65 (16%) [0.45, 0.84]	91 (33%) [53, 155]	4.9 (35%) [1.8, 8.3]	1.7 (34%) [0.9, 3.3]

\* AUC = Single dose AUC<sub>0-∞</sub>

\*\* In this data set, “pre-term” is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days)

\*\*\* In this data set, “full-term” is defined as ≥ 34 weeks gestational age

† Dose of 10 mg/kg

‡ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg

§ Dose normalized to 600 mg

$C_{max}$  = Maximum plasma concentration;  $V_{ss}$  = Volume of distribution; AUC = Area under concentration-time curve;

$T_{1/2}$  = Apparent elimination half-life; CL = Systemic clearance normalized for body weight

## Gender

Females have a slightly lower volume of distribution of linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

## Renal Impairment

The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal impairment; however, the two primary metabolites of linezolid accumulate in patients with renal impairment, with the amount of accumulation increasing with the severity of renal dysfunction. The pharmacokinetics of linezolid and its two metabolites have also been studied in patients with end-stage renal disease (ESRD) receiving hemodialysis. 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. Both linezolid and the two metabolites are eliminated by hemodialysis. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Approximately 30% of a dose was eliminated in a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after hemodialysis.

## Hepatic Impairment

The pharmacokinetics of linezolid are not altered in patients (n=7) with mild-to-moderate hepatic impairment (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for patients with mild-to-moderate hepatic impairment. The pharmacokinetics of linezolid in patients with severe hepatic impairment have not been evaluated.

## Drug Interactions

### Drugs Metabolized by Cytochrome P450

Linezolid is not an inducer of cytochrome P450 (CYP450) in rats. In addition, linezolid does not inhibit the activities of clinically significant human CYP isoforms (e.g., 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, linezolid is not expected to affect the pharmacokinetics of other drugs metabolized by these major enzymes. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S) warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

### Antibiotics

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.

## Antioxidants

The potential for drug-drug interactions with linezolid and the antioxidants Vitamin C and Vitamin E was studied in healthy volunteers. No linezolid dose adjustment is recommended during coadministration with Vitamin C or Vitamin E.

## Strong CYP 3A4 Inducers

Rifampin: The effect of rifampin on the pharmacokinetics of linezolid was evaluated in a study of 16 healthy adult males. Co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid  $C_{max}$  [90% CI, 15% - 27%] and a 32% decrease in linezolid  $AUC_{0-12}$  [90% CI, 27% - 37%]. The clinical significance of this interaction is unknown. The mechanism of this interaction is not fully understood and may be related to the induction of hepatic enzymes. Other strong inducers of hepatic enzymes (e.g. carbamazepine, phenytoin, phenobarbital) could cause a similar or smaller decrease in linezolid exposure.

## Monoamine Oxidase Inhibition

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

## Adrenergic Agents

Some individuals receiving linezolid may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response.

Tyramine: A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content.

Pseudoephedrine HCl or phenylpropanolamine HCl: A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects [see Warnings and Precautions and Drug Interactions]. A similar study has not been conducted in hypertensive patients.

## Serotonergic Agents

Dextromethorphan: 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.

## **Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after authorization of the medicinal product is Important. It allows continued monitoring of the benefit/risk balance of the medicinal Product. Healthcare professionals are asked to report any suspected adverse reactions via:

Also you can report via:

Egyptian Pharmaceutical Vigilance Center (EPVC)

21 Abd El Aziz Al Soud Street. El-Manial, Cairo, Egypt.

E-mail: [pv.center@eda.mohip.gov.eg](mailto:pv.center@eda.mohip.gov.eg)

Fax Number: +2 02 23684194

Telephone: +2 02 (23648046, 23640368, 23684381, 23684288), Extension No. 1303

### **LIST OF EXCIPENTS**

Citric acid anhydrous, sodium citrate dihydrate, sodium chloride, sodium hydroxide, hydrochloric acid and water for Infusion.

### **Nature and contents of container**

LDPE plastic bottle with Euro head cap (autoclavable consist of white HDPE plastic cap and grey polyisoprene rubber disk) contains 300 ml solution in hard AL bag with inner leaflet.

### **Special precautions for storage**

Store at temperature not exceeding 30 ° C. to be used immediately after opening.

**Manufactured by:**

**Averroes pharma for pharmaceutical industries**

**Keep medicines out of reach of children**

