Oxazolid 100 mg/5ml Dry powder for oral suspension

Indication and usage

Oxazolid is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Oxazolid 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*].

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*. Linezolid 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.

Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Oxazolid and other antibacterial drugs, Oxazolid should be used only to treat or prevent 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 linezolid 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 Oxazolid formulations for the treatment of infections is described in Table.

Table 1. Dosage Guidelines for Oxazolid

Infection*	**Dosage and Route of Administration**	**Recommended Duration of Treatment (consecutive days)**
	Pediatric Patients† (Birth through 11 Years of Age)	
Nosocomial pneumonia	10 mg/kg intravenously or oral‡ every 8 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 intravenously or oral‡ every 8 hours	14 to 28
Uncomplicated skin and skin structure infections	less than 5 yrs: 10 mg/kg oral‡ every 8 hours 5-11 yrs: 10 mg/kg oral‡ every 12 hours	10 to 14

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

† **Neonates less than**7 **days**: Most pre-term neonates less than7 days of age (gestational age less than34 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*].

‡ Oral dosing using either Oxazolid Tablets or Oxazolid for Oral Suspension [*see How Supplied/Storage*].

No dose adjustment is necessary when switching from intravenous to oral administration.

Constitution of Oral Suspension

Oxazolid for Oral Suspension is supplied as a powder for constitution. Gently tap bottle to loosen powder. Add a total of 123 mL distilled water in two portions. After adding the first half, shake vigorously to wet all of the powder. Then add the second half of the water and shake vigorously to obtain a uniform suspension. After constitution, each 5 mL of the suspension contains 100 mg of linezolid. Before using, gently mix by inverting the bottle 3 to 5 times. Do not shake. Store constituted suspension at temperature not exceed 30°C in a dry place . Use within 7 days after constitution.

DOSAGE FORMS AND STRENGTHS

Oxazolid for Oral Suspension: white to off-white homogenous powder. When constituted as directed, each bottle will contain 150 mL of a suspension providing the equivalent of 100 mg of linezolid per each 5 mL.

CONTRAINDICATIONS

Hypersensitivity

Oxazolid formulations are 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.

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 linezolid, 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 linezolid 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 Oxazolid for extended periods (≥ 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with Oxazolid. If peripheral or optic neuropathy occurs, the continued use of Oxazolid 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 [*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).

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 [(21.5%) vs.
(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*].

Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Oxazolid, 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) [*see Drug Interactions and Clinical Pharmacology*]**.**

Lactic Acidosis

Lactic acidosis has been reported with the use of linezolid. 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 Oxazolid 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, 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 Oxazolid 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

Pediatric Patients:

Table 3. Incidence (%) of Treatment-Emergent Adverse Reactions Occurring in > 1% of Pediatric Patients (and >1 Patient)

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

Laboratory Abnormalities:

Table 6. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Hematology Laboratory Value

Laboratory Assay
Hemoglobin (g/dL)
Platelet count (x $10^3/mm^3$)
WBC (x $10^3/mm^3$)
Neutrophils (x $10^3/mm^3$)

* <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline;

<75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

† Patients 5 through 11 years of age received linezolid 10 mg/kg by mouth every 12 hours . Patients 12 years or older received linezolid 600 mg by mouth every 12 hours .

Table 7. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Serum Chemistry Laboratory Value

Laboratory Assay
ALT (U/L)
Lipase (U/L)
Amylase (U/L)
Total bilirubin (mg/dL)
Creatinine (mg/dL)

*>2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

† Patients 5 through 11 years of age received linezolid 10 mg/kg by mouth every 12 hours. Patients 12 years or older received linezolid 600 mg mouth every 12 hours

Other adverse reactions

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported [*see Warnings and Precautions*]. Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with linezolid [*see Warnings and Precautions*]. Lactic acidosis has been reported with the use of linezolid [*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 linezolid [*see Warnings and Precautions*]. Convulsions have been reported with the use of linezolid [*see Warnings and Precautions*]. 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 been reported [*see Warnings and Precautions*].

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors

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

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

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

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.

Pediatric Use

The safety and effectiveness of Linezolid 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

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.

DESCRIPTION

Oxazolid for Oral Suspension is supplied as white to off white homogenous powder for constitution into a suspension for oral administration. Following constitution, each 5 mL contains 100 mg of linezolid. Inactive ingredients are mannitol, xanthan gum, avicel RC591, sodium citrate, citric acid, aerosil 200, Orange flavor powder, sodium benzoate, , and sucrose.

CLINICAL PHARMACOLOGY

Mechanism of Action

Linezolid is an antibacterial drug [(see *Microbiology)*].

Pharmacodynamics

At both the 600 mg and 1200 mg Linezolid 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 oral and intravenous doses are summarized in Table 8. Plasma concentrations of linezolid at steady-state after oral doses of 600 mg given every 12 hours are shown in Figure 1.

Table 8. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	C_{max} mcg/mL	C_{min} mcg/mL	T_{max} hrs	AUC * mcg•h/mL	$t_{1/2}$ hrs	CL mL/min

600 mg tablet						
single dose	12.70 (3.96)	---	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
every 12 hours	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg oral suspension						
single dose	11.00 (2.76)	---	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)

* AUC for single dose = $AUC_{0-\infty}$; for multiple dose = $AUC_{0-\tau}$

† Data dose-normalized from 375 mg

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

C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; T_{max} = Time to C_{max}; AUC = Area under concentration-time curve; $t_{1/2}$ = 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_{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 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 9 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 (2)*].

Table 9. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

Age Group	C_{max} mcg/mL	V_{ss} L/kg	AUC* mcg•h/mL	t 1/2 hrs	CL mL/min/kg
Neonatal Patients	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]
Pre-term** < 1 week (N=9)†	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]
Full-term*** < 1 week (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]
Full-term*** ≥ 1 week to ≤ 28 days (N=10)†					
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 $AUC_{0-\infty}$

** 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

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 (see Table 10). The pharmacokinetics of linezolid and its two metabolites have also been studied in patients with end-stage renal disease (ESRD) receiving hemodialysis. 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. 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 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 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. Subjects were administered a 600 mg oral dose of linezolid on Day 1, and another 600 mg dose of linezolid on Day 8. On Days 2-9, subjects were given either Vitamin C (1000 mg/day) or Vitamin E (800 IU/ day). The $AUC_{0-\infty}$ of linezolid increased 2.3% when co-administered with Vitamin C and 10.9% when co administered with Vitamin E. No linezolid dose adjustment is recommended during co-administration 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. Volunteers were administered oral linezolid 600 mg twice daily for 5 doses with and without rifampin 600 mg once daily for 8 days. 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 [*see Patient Counseling Information*].

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. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg every 12 hours for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments. Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2 to 3 hours after the second dose of PPA or PSE, and returned to baseline 2 to 3 hours after peak. The results of the PPA study follow, showing the mean (and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg (range: 20-52 mm Hg) and 38 mm Hg (range: 18-79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively.

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, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

Microbiology

Mechanism of Action

Linezolid is a synthetic antibacterial agent of the oxazolidinone class, 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 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 essential for bacterial reproduction. 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.

Mechanisms of Resistance

In vitro studies have shown that point mutations in the 23S rRNA are associated with linezolid resistance. Reports of vancomycin-resistant *Enterococcus faecium* becoming resistant to linezolid during its clinical use have been published. There are reports of *Staphylococcus aureus* (methicillin-resistant) developing resistance to linezolid during clinical use. 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. Also linezolid resistance in staphylococci mediated by the enzyme methyltransferase has been reported. This resistance is mediated by the *cfr* (chloramphenicol-florfenicol) gene located on a plasmid which is transferable between staphylococci.

Interaction with Other Antimicrobial Drugs

In vitro studies have demonstrated additivity or indifference between linezolid and vancomycin, gentamicin, rifampin, imipenem-cilastatin, aztreonam, ampicillin, or streptomycin.

Linezolid has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections. [See Indications and Usage].

Gram-positive bacteria

Enterococcus faecium (vancomycin-resistant isolates only)

Staphylococcus aureus (including methicillin-resistant isolates)

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Greater than 90% of the following bacteria exhibit an in vitro MIC less than or equal to the linezolid-susceptible breakpoint for organisms of similar genus shown in Table 12. The safety and effectiveness of linezolid in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

Enterococcus faecalis (including vancomycin-resistant isolates)

Enterococcus faecium (vancomycin-susceptible isolates)

Staphylococcus epidermidis (including methicillin-resistant isolates) *Staphylococcus haemolyticus*

Viridans group streptococci

Gram-negative bacteria

Pasteurella multocida

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Storage:

Store at temperature not exceeding 30˚C in dry place to be used within 7 days after reconstitution .

Pack:

Carton box containing an amber glass (Tybe III) bottle with plastic (HDPE) Screw cap Contains 76.05 mg powder to give 150 ml suspension after reconstitution and an inner leaflet .

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