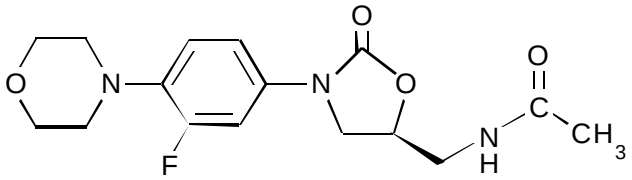
ZYVOX™
linezolid injection
linezolid tablets
linezolid for oral suspension

DESCRIPTION

ZYVOX I.V. Injection, ZYVOX Tablets, and ZYVOX for Oral Suspension contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide.

The empirical formula is $C_{16}H_{20}FN_3O_4$. Its molecular weight is 337.35, and its chemical structure is represented below:



ZYVOX I.V. Injection is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each mL contains 2 mg of linezolid. Inactive ingredients are sodium citrate, citric acid, and dextrose in an aqueous vehicle for intravenous administration. The sodium (Na^+) content is 0.38 mg/mL (5 mEq per 300-mL bag; 3.3 mEq per 200-mL bag; and 1.7 mEq per 100-mL bag).

ZYVOX Tablets for oral administration contain 400 mg or 600 mg linezolid as film-coated compressed tablets. Inactive ingredients are corn starch, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and carnauba wax. The sodium (Na^+) content is 1.95 mg per 400-mg tablet and 2.92 mg per 600-mg tablet (0.1 mEq per tablet, regardless of strength).

ZYVOX for Oral Suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration. Following constitution, each 5 mL contains 100 mg of linezolid. Inactive ingredients are sucrose, citric acid, sodium citrate, microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum, mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors (see **PRECAUTIONS, Information for Patients**). The sodium (Na^+) content is 8.52 mg per 5 mL (0.4 mEq per 5 mL).

CLINICAL PHARMACOLOGY

Pharmacokinetics

The mean pharmacokinetic parameters of linezolid after single and multiple oral and intravenous doses are summarized in Table 1. Plasma concentrations of linezolid at steady-state after oral doses of 600 mg given every 12 hours (q12h) are shown in Figure 1.

Table 1. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid

Dose of Linezolid	C_{max} µg/mL	C_{min} µg/mL	T_{max} hrs	AUC * µg • h/mL	$t_{1/2}$ hrs	CL mL/min
400 mg tablet						
single dose †	8.10 (1.83)	---	1.52 (1.01)	55.10 (25.00)	5.20 (1.50)	146 (67)
every 12 hours	11.00 (4.37)	3.08 (2.25)	1.12 (0.47)	73.40 (33.50)	4.69 (1.70)	110 (49)
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 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)
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, IV 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

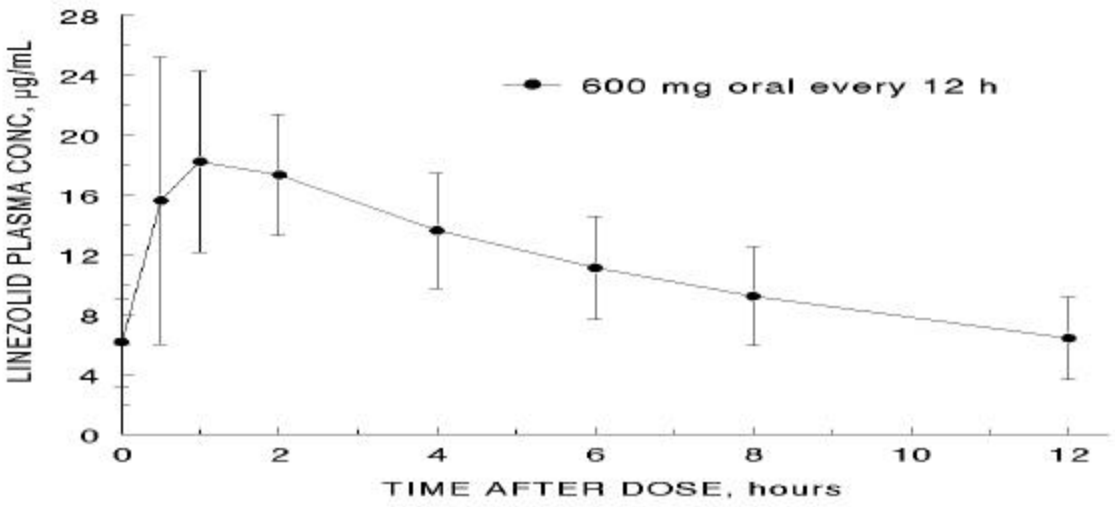


Figure 1. Plasma Concentrations of Linezolid at Steady-State Following Oral Dosing Every 12 Hours (Mean ± Standard Deviation, n=16)

Absorption: Linezolid is rapidly and 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 $AUC_{0-\infty}$ values 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 for 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 B is mediated by a non-enzymatic chemical oxidation mechanism in vitro. Linezolid is not an inducer of cytochrome P450 (CYP) in rats, and it has been demonstrated from in vitro studies that linezolid is not detectably metabolized by human cytochrome P450 and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4).

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 renal clearance of linezolid is low (average 40 mL/min) and suggests net tubular reabsorption. Virtually no linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B, and 3% as metabolite A.

A small degree of nonlinearity in clearance was observed with increasing doses of linezolid, which appears to be due to lower renal and nonrenal clearance of linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

Special Populations

Geriatric: 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: Currently, there are limited data on the pharmacokinetics of linezolid during multiple dosing in pediatric patients of all ages. No data have been collected in infants younger than 3 months of age.

Pharmacokinetic information indicates that pediatric patients dosed with 10 mg/kg IV have a similar C_{max} but a higher average clearance when corrected by body weight, and shorter apparent elimination half-life than adults receiving 625 mg of linezolid. Pediatric dosing regimens that provide a pharmacokinetic profile similar to adults have not been determined. Studies using doses higher than 10 mg/kg or dosing more frequently than every 12 hours have not been conducted in pediatric patients.

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. After a 600-mg dose, mean oral clearance is approximately 38% lower in females than in males. However, there are no significant gender differences in mean apparent elimination-rate constant or half-life. 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 Insufficiency: The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal insufficiency; however, the two primary metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction (see Table 2). The clinical significance of accumulation of these two metabolites has not been determined in patients with severe renal insufficiency. Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal insufficiency. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites. Both linezolid and the two metabolites are eliminated by dialysis.
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 dialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after hemodialysis.

Table 2. Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Patients with Varying Degrees of Renal Insufficiency After a Single 600-mg Oral Dose of Linezolid

Parameter	Healthy Subjects CL_{CR} > 80 mL/min	Moderate Renal Impairment 30 < CL_{CR} < 80 mL/min	Severe Renal Impairment 10 < CL_{CR} < 30 mL/min	Hemodialysis-Dependent	
				Off Dialysis*	On Dialysis
Linezolid					
$AUC_{0-\infty}$, µg h/mL	110 (22)	128 (53)	127 (66)	141 (45)	83 (23)
$t_{1/2}$, hours	6.4 (2.2)	6.1 (1.7)	7.1 (3.7)	8.4 (2.7)	7.0 (1.8)
Metabolite A					
AUC_{0-48}, µg h/mL	7.6 (1.9)	11.7 (4.3)	56.5 (30.6)	185 (124)	68.8 (23.9)
$t_{1/2}$, hours	6.3 (2.1)	6.6 (2.3)	9.0 (4.6)	NA	NA
Metabolite B					
AUC_{0-48}, µg h/mL	30.5 (6.2)	51.1 (38.5)	203 (92)	467 (102)	239 (44)
$t_{1/2}$, hours	6.6 (2.7)	9.9 (7.4)	11.0 (3.9)	NA	NA

* between hemodialysis sessions
NA = Not applicable

Hepatic Insufficiency: The pharmacokinetics of linezolid are not altered in patients (n=7) with mild-to-moderate hepatic insufficiency (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 insufficiency. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency have not been evaluated.

Drug-Drug Interactions

Drugs Metabolized by Cytochrome P450: Linezolid is not an inducer of cytochrome P450 (CYP) in rats. It is not detectably metabolized by human cytochrome P450 and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-induced drug interactions are expected with linezolid. 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.

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: 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 **PRECAUTIONS**, **Information for Patients**).

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 **PRECAUTIONS**, **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 q12h 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: 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. The effects of other serotonin re-uptake inhibitors have not been studied.

MICROBIOLOGY

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 strains.

In clinical trials, resistance to linezolid developed in 6 patients infected with *E. faecium* (4 patients received 200 mg q12h, lower than the recommended dose, and 2 patients received 600 mg q12h). In a compassionate use program, resistance to linezolid developed in 8 patients with *E. faecium* and in 1 patient with *E. faecalis*. All patients had either unremoved prosthetic devices or undrained abscesses. Resistance to linezolid occurs in vitro at a frequency of 1×10^{-9} to 1×10^{-11}. In vitro studies have shown that point mutations in the 23S rRNA are associated with linezolid resistance. Resistance to linezolid has not been seen in clinical trials in patients infected with *Staphylococcus* spp. or *Streptococcus* spp., including *S. pneumoniae*.

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, as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecium (vancomycin-resistant strains only)
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

The following in vitro data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for linezolid. However, the safety and effectiveness of linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms
Enterococcus faecalis (including vancomycin-resistant strains)
Enterococcus faecium (vancomycin-susceptible strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Streptococcus pneumoniae (penicillin-resistant strains)
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms
Pasteurella multocida

Susceptibility Testing Methods
NOTE: Susceptibility testing by dilution methods requires the use of linezolid susceptibility powder.

When available, the results of in vitro susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of linezolid powder. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg of linezolid to test the susceptibility of microorganisms to linezolid. The disk diffusion interpretive criteria are provided in Table 3.

Table 3. Susceptibility Interpretive Criteria for Linezolid

Pathogen	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in ■g/mL)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Enterococcus spp	≤ 2	4	≥8	≥ 23	21-22	≤20
Staphylococcus spp [a]	≤4	---	---	≥ 21	---	---
Streptococcus pneumoniae [a]	≤2[b]	---	---	≥ 21[c]	---	---
Streptococcus spp other than *S pneumoniae* [a]	≤2[b]	---	---	≥ 21[c]	---	---

[a] The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding test results suggestive of a "nonsusceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

[b] These interpretive standards for *S. pneumoniae* and *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

[c] These zone diameter interpretive standards are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20 to 24 hours.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard linezolid powder should provide the following range of values noted in Table 4. **NOTE:** Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 4. Acceptable Quality Control Ranges for Linezolid to be Used in Validation of Susceptibility Test Results

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (MIC in ■g/mL)	Disk Diffusion (Zone Diameters in mm)
Enterococcus faecalis ATCC 29212	1 - 4	Not applicable
Staphylococcus aureus ATCC 29213	1 - 4	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	27 - 31
Streptococcus pneumoniae ATCC 49619[d]	0.50 - 2[e]	28 - 34[f]

[d] This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

[e] This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

[f] This quality control zone diameter range is applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20 to 24 hours.

INDICATIONS AND USAGE

ZYVOX formulations are indicated for the treatment of adult patients with the following infections caused by susceptible strains of the designated microorganisms (see **DOSAGE AND ADMINISTRATION**).

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia (see **CLINICAL STUDIES**).

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

Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes,* or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of diabetic foot and decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include gram-negative organisms (see **CLINICAL STUDIES**).

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

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

Due to concerns about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with ZYVOX in the outpatient setting.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to linezolid. Therapy may be instituted empirically while awaiting the results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

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

WARNINGS
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ZYVOX, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicated that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*.

PRECAUTIONS
General
The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

Thrombocytopenia
Thrombocytopenia has been reported in patients receiving linezolid (see **ADVERSE REACTIONS**). Platelet counts should be monitored in patients who are at increased risk for bleeding, who have pre-existing thrombocytopenia, who receive concomitant medications that may decrease platelet count or function, or who may require longer than 2 weeks of linezolid therapy.

Information for Patients
Patients should be advised that:

- ZYVOX may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. [4,5]
- They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants.
- They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants.
- *Phenylketonurics*: Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist.

Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug-Drug Interactions)
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 ZYVOX 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.

Serotonergic Agents: Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in phase 1, 2 or 3 studies. Since there is limited experience with concomitant administration of linezolid and serotonergic agents, physicians should be alert to the possibility of signs and symptoms of serotonin syndrome (e.g., hyperpyrexia, and cognitive dysfunction) in patients receiving such concomitant therapy.

Drug-Laboratory Test Interactions
There are no reported drug-laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Although lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of linezolid, no mutagenic or clastogenic potential was found in a battery of tests, including the Ames and AS52 assays, an in vitro unscheduled DNA synthesis (UDS) assay, an in vitro chromosome aberration assay in human lymphocytes, and an in vivo mouse micronucleus assay.

Linezolid did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ≥ 50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). Epithelial cell hypertrophy in the epididymis may have contributed to the decreased fertility by affecting sperm maturation. Similar epididymal changes were not seen in dogs. Although the concentrations of sperm in the testes were in the normal range, the concentrations in the cauda epididymis were decreased, and sperm from the vas deferens had decreased motility.

Mildly decreased fertility occurred in juvenile male rats treated with linezolid through most of their period of sexual development (50 mg/kg/day from days 7 to 36 of age, and 100 mg/kg/day from days 37 to 55 of age, with exposures ranging from 0.4-fold to 1.2-fold that expected in humans based on AUCs). No histopathological evidence of adverse effects was observed in the male reproductive tract.

Pregnancy
Teratogenic Effects. Pregnancy Category C: Linezolid was not teratogenic in mice or rats at exposure levels 4-fold (in mice) or equivalent to (in rats) 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. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects
In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (4-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion.

In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.13- to 0.64-fold the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day.

When female rats were treated with 50 mg/kg/day (0.64-fold the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss, with a corresponding decrease in fertility.

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 ZYVOX is administered to a nursing woman.

Pediatric Use
Although it may be possible to extrapolate adult efficacy to pediatric patients, the appropriate dose and safety of ZYVOX have not been established in this population. Drug clearance of ZYVOX is increased in pediatric patients compared to adults, resulting in a shorter half-life (see **CLINICAL PHARMACOLOGY, Pediatric**). Pediatric dosing regimens that provide a pharmacokinetic profile similar to adults have not been determined.

Geriatric Use
Of the 2046 patients treated with ZYVOX in phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

ANIMAL PHARMACOLOGY
Dose- and time-dependent myelosuppression, as evidenced by bone marrow hypocellularity, decreased hematopoiesis, and decreased levels of circulating erythrocytes, leukocytes, and platelets, has been seen in animal studies. The hematopoietic effects occurred at doses of 40 and 80 mg/kg/day in dogs and rats, respectively (at exposures approximately 0.6 times in the dog and equal in the rat to the expected human exposure based on AUC). Hematopoietic effects were reversible, although in some studies reversal was incomplete within the duration of the recovery period.

ADVERSE REACTIONS
The safety of ZYVOX formulations was evaluated in 2046 patients enrolled in seven phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. Table 5 shows the incidence of adverse events reported in at least 2% of patients in these trials. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%).

Table 5. Incidence (%) of Adverse Events Reported in ³ 2% of Patients in Comparator-Controlled Clinical Trials with ZYVOX

Event	ZYVOX (n=2046)	All Comparators * (n=2001)
Diarrhea	8.3	6.3

Headache	6.5	5.5
Nausea	6.2	4.6
Vomiting	3.7	2.0
Insomnia	2.5	1.7
Constipation	2.2	2.1
Rash	2.0	2.2
Dizziness	2.0	1.9
Fever	1.6	2.1

* Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Other adverse events reported in phase 2 and phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration.

Table 6 shows the incidence of drug-related adverse events reported in at least 1% of patients in these trials by dose of ZYVOX.

Table 6. Incidence of Drug-Related Adverse Events Occurring in >1% of Patients Treated with ZYVOX in Comparator-Controlled Clinical Trials

Adverse Event	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg PO q12h (n=548)	Clarithromycin 250 mg PO q12h (n=537)	ZYVOX 600 mg q12h (n=1498)	All Other Comparators* (n=1464)
% of patients with 1 drug-related adverse event	25.4	19.6	20.4	14.3
% of patients discontinuing due to drug-related adverse events†	3.5	2.4	2.1	1.7
Diarrhea	5.3	4.8	4.0	2.7
Nausea	3.5	3.5	3.3	1.8
Headache	2.7	2.2	1.9	1.0
Taste alteration	1.8	2.0	0.9	0.2
Vaginal moniliasis	1.6	1.3	1.0	0.4
Fungal infection	1.5	0.2	0.1	<0.1
Abnormal liver function tests	0.4	0	1.3	0.5
Vomiting	0.9	0.4	1.2	0.4
Tongue discoloration	1.1	0	0.2	0
Dizziness	1.1	1.5	0.4	0.3
Oral moniliasis	0.4	0	1.1	0.4

* Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

† The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

Laboratory Changes

ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In phase 3 comparator-controlled trials, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. Thrombocytopenia associated with the use of ZYVOX 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. No related clinical adverse events were identified in phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **PRECAUTIONS**).

Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The incidence of patients with at least one substantially abnormal hematologic or serum chemistry value is presented in Tables 7 and 8.

.

Table 7. Percent of Patients who Experienced at Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg q12h	Clarithromycin 250 mg q12h	ZYVOX 600 mg q12h	All Other Comparators†
Hemoglobin (g/dL)	0.9	0.0	7.1	6.6
Platelet count (x 10^3/mm^3)	0.7	0.8	3.0	1.8
WBC (x 10^3/mm^3)	0.2	0.6	2.2	1.3
Neutrophils (x 10^3/mm^3)	0.0	0.2	1.1	1.2

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

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Table 8. Percent of Patients who Experienced at Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg q12h	Clarithromycin 250 mg q12h	ZYVOX 600 mg q12h	All Other Comparators†
AST (U/L)	1.7	1.3	5.0	6.8
ALT (U/L)	1.7	1.7	9.6	9.3
LDH (U/L)	0.2	0.2	1.8	1.5
Alkaline phosphatase (U/L)	0.2	0.2	3.5	3.1
Lipase (U/L)	2.8	2.6	4.3	4.2
Amylase (U/L)	0.2	0.2	2.4	2.0
Total bilirubin (mg/dL)	0.2	0.0	0.9	1.1
BUN (mg/dL)	0.2	0.0	2.1	1.5
Creatinine (mg/dL)	0.2	0.0	0.2	0.6

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

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

OVERDOSAGE

In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. 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.

DOSAGE AND ADMINISTRATION

The recommended dosage for ZYVOX formulations for the treatment of infections is described in Table 9. Doses of ZYVOX are administered every twelve hours (q12h).

Table 9. Dosage Guidelines for ZYVOX

Infection*	Dosage and Route of Administration	Recommended Duration of Treatment (consecutive days)
Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia	600 mg IV or oral† q12h	14 to 28
Nosocomial pneumonia	600 mg IV or oral† q12h	10 to 14
Complicated skin and skin structure infections		
Community-acquired pneumonia, including concurrent bacteremia		
Uncomplicated skin and skin structure infections	400 mg oral† q12h	10 to 14

* due to the designated pathogens (see **INDICATIONS AND USAGE**)

† oral dosing using either ZYVOX Tablets or ZYVOX for Oral Suspension

Patients with infection due to MRSA should be treated with ZYVOX 600 mg q12h.

In controlled clinical trials, the protocol-defined duration of treatment for all infections ranged from 7 to 28 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response.

No dose adjustment is necessary when switching from intravenous to oral administration. Patients whose therapy is started with ZYVOX I.V. Injection may be switched to either ZYVOX Tablets or Oral Suspension at the discretion of the physician, when clinically indicated.

Intravenous Administration

ZYVOX I.V. Injection is supplied in single-use, ready-to-use infusion bags (see **HOW SUPPLIED** for container sizes). 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.

ZYVOX 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 ZYVOX 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. In particular, physical incompatibilities resulted when ZYVOX 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 ZYVOX I.V. Injection 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 ZYVOX I.V. Injection with an infusion solution compatible with ZYVOX I.V. Injection and with any other drug(s) administered via this common line (see **Compatible Intravenous Solutions**).

Compatible Intravenous Solutions

5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP

Keep the infusion bags in the overwrap until ready to use. Store at room temperature. Protect from freezing. ZYVOX I.V. Injection may exhibit a yellow color that can intensify over time without adversely affecting potency.

Constitution of Oral Suspension
ZYVOX for Oral Suspension is supplied as a powder/granule 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 room temperature. Use within 21 days after constitution.

HOW SUPPLIED
Injection
ZYVOX I.V. Injection is available in single-use, ready-to-use flexible plastic infusion bags in a foil laminate overwrap. The infusion bags and ports are latex-free. The infusion bags are available in the following package sizes:

100 mL bag (200 mg linezolid)	NDC 0009-5137-01
200 mL bag (400 mg linezolid)	NDC 0009-5139-01
300 mL bag (600 mg linezolid)	NDC 0009-5140-01

Tablets
ZYVOX Tablets are available as follows:

400 mg (white, oblong, film-coated tablets printed with "ZYVOX 400mg")

100 tablets in HDPE bottle	NDC 0009-5134-01
20 tablets in HDPE bottle	NDC 0009-5134-02
Unit dose packages of 30 tablets	NDC 0009-5134-03

600 mg (white, capsule-shaped, film-coated tablets printed with "ZYVOX 600 mg")

100 tablets in HDPE bottle	NDC 0009-5135-01
20 tablets in HDPE bottle	NDC 0009-5135-02
Unit dose packages of 30 tablets	NDC 0009-5135-03

Oral Suspension
ZYVOX for Oral Suspension is available as a dry, white to off-white, orange-flavored granule/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. ZYVOX for Oral Suspension is supplied as follows:

100 mg/5 mL in 240-mL glass bottles	NDC 0009-5136-01

Storage of ZYVOX Formulations
Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature]. Protect from light. Keep bottles tightly closed to protect from moisture. It is recommended that the infusion bags be kept in the overwrap until ready to use. Protect infusion bags from freezing.

CLINICAL STUDIES
Vancomycin-Resistant Enterococcal Infections
Adult patients with documented or suspected vancomycin-resistant enterococcal infection were enrolled in a randomized, multi-center, double-blind trial comparing a high dose of ZYVOX (600 mg q12h IV or orally) with a low dose of ZYVOX (200 mg q12h IV or orally) for 7 to 28 days. Patients could receive concomitant aztreonam or aminoglycosides. There were 79 patients randomized to high-dose linezolid and 66 to low-dose linezolid. The intent-to-treat (ITT) population with documented vancomycin-resistant enterococcal infection at baseline consisted of 65 patients in the high-dose arm and 52 in the low-dose arm.

The cure rates for the ITT population with documented vancomycin-resistant enterococcal infection at baseline are presented in Table 10 by source of infection. These cure rates do not include patients with missing or indeterminate

outcomes. The cure rate was higher in the high-dose arm than in the low-dose arm, although the difference was not statistically significant at the 0.05 level.

Table 10. Cure Rates at the Test-of-Cure Visit for ITT Patients with Documented Vancomycin-Resistant Enterococcal Infections at Baseline

Source of Infection	Cured	
	ZYVOX 600 mg q12h n/N (%)	ZYVOX 200 mg q12h n/N (%)
Any site	39/58 (67)	24/46 (52)
Any site with associated bacteremia	10/17 (59)	4/14 (29)
Bacteremia of unknown origin	5/10 (50)	2/7 (29)
Skin and skin structure	9/13 (69)	5/5 (100)
Urinary tract	12/19 (63)	12/20 (60)
Pneumonia	2/3 (67)	0/1 (0)
Other*	11/13 (85)	5/13 (39)

* Includes sources of infection such as hepatic abscess, biliary sepsis, necrotic gall bladder, pericolonic abscess, pancreatitis, and catheter-related infection.

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a randomized, multi-center, double-blind trial. Patients were treated for 7 to 21 days. One group received ZYVOX I.V. Injection 600 mg every twelve hours (q12h), and the other group received vancomycin 1 g q12h intravenously (IV). Both groups received concomitant aztreonam (1 to 2 g every 8 hours IV), which could be continued if clinically indicated. There were 203 linezolid-treated and 193 vancomycin-treated patients enrolled in the study. One hundred twenty-two (60%) linezolid-treated patients and 103 (53%) vancomycin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 57% for linezolid-treated patients and 60% for vancomycin-treated patients. The cure rates in clinically evaluable patients with ventilator-associated pneumonia were 47% for linezolid-treated patients and 40% for vancomycin-treated patients. A modified intent-to-treat (MITT) analysis of 94 linezolid-treated patients and 83 vancomycin-treated patients included subjects who had a pathogen isolated before treatment. The cure rates in the MITT analysis were 57% in linezolid-treated patients and 46% in vancomycin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 11.

Table 11. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Patients with Nosocomial Pneumonia

Pathogen	Cured	
	ZYVOX n/N (%)	Vancomycin n/N (%)
Staphylococcus aureus	23/38 (61)	14/23 (61)
Methicillin-resistant *S. aureus*	13/22 (59)	7/10 (70)
Streptococcus pneumoniae	9/9 (100)	9/10 (90)

Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections were enrolled in a randomized, multi-center, double-blind, double-dummy trial comparing study medications administered IV followed by medications given orally for a total of 10 to 21 days of treatment. One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX Tablets 600 mg q12h; the other group received oxacillin 2 g every 6 hours (q6h) IV followed by dicloxacillin 500 mg q6h orally. Patients could receive concomitant aztreonam if clinically indicated. There were 400 linezolid-treated and 419 oxacillin-treated patients enrolled in the study. Two hundred forty-five (61%) linezolid-treated patients and 242 (58%) oxacillin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 90% in linezolid-treated patients and 85% in oxacillin-treated patients. A modified intent-to-treat (MITT) analysis of 316 linezolid-treated patients and 313 oxacillin-treated patients included subjects who met all criteria for study entry. The

cure rates in the MITT analysis were 86% in linezolid-treated patients and 82% in oxacillin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 12.

Table 12. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Patients with Complicated Skin and Skin Structure Infections

Pathogen	Cured	
	ZYVOX n/N (%)	Oxacillin/Dicloxacillin n/N (%)
Staphylococcus aureus	73/83 (88)	72/84 (86)
Methicillin-resistant *S. aureus*	2/3 (67)	0/0 (-)
Streptococcus agalactiae	6/6 (100)	3/6 (50)
Streptococcus pyogenes	18/26 (69)	21/28 (75)

A separate study provided additional experience with the use of linezolid in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. This was a randomized, open-label trial in hospitalized adult patients with documented or suspected MRSA infection.

One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX Tablets 600 mg q12h. The other group of patients received vancomycin 1 g q12h IV. Both groups were treated for 7 to 28 days, and could receive concomitant aztreonam or gentamicin if clinically indicated. The cure rates in microbiologically evaluable patients with MRSA skin and skin structure infection were 26/33 (79%) for linezolid-treated patients and 24/33 (73%) for vancomycin-treated patients.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests. Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January 2000.
3. National Committee for Clinical Laboratory Standards. Tenth Informational Supplement. Approved NCCLS Document M100-S10, Vol. 20, No. 1, NCCLS, Wayne, PA, January 2000.
4. Walker, SE et al. Tyramine content of previously restricted foods in monoamine oxidase inhibitor diets. Journal of Clinical Psychopharmacology 1996;16 (5):383-388.
5. DaPrada, M et al. On tyramine, food, beverages and the reversible MAO inhibitor moclobemide. 1988; [Supplement] 26:31-56.

Rx only

US Patent No. 5,688,792

Injection

Manufactured for: Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001

By: Fresenius Kabi Norge AS
Halden, Norway

Tablets and Oral Suspension
Manufactured by: Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001

[Date and copy codes]