

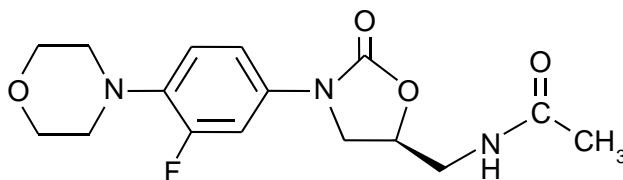
1
2 **ZYVOX[®]**
3 **(linezolid) injection**
4 **(linezolid) tablets**
5 **(linezolid) for oral**
6 **suspension**
7
8

9 To reduce the development of drug-resistant bacteria and maintain the effectiveness of
10 ZYVOX formulations and other antibacterial drugs, ZYVOX should be used only to treat
11 or prevent infections that are proven or strongly suspected to be caused by bacteria.

12
13 **DESCRIPTION**

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

18
19 The empirical formula is C₁₆H₂₀FN₃O₄. Its molecular weight is 337.35, and its chemical
20 structure is represented below:
21



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

27
28 ZYVOX Tablets for oral administration contain 400 mg or 600 mg linezolid as film-coated
29 compressed tablets. Inactive ingredients are corn starch, microcrystalline cellulose,
30 hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, hypromellose,
31 polyethylene glycol, titanium dioxide, and carnauba wax. The sodium (Na⁺) content is 1.95
32 mg per 400-mg tablet and 2.92 mg per 600-mg tablet (0.1 mEq per tablet, regardless of
33 strength).
34

35 ZYVOX for Oral Suspension is supplied as an orange-flavored granule/powder for
 36 constitution into a suspension for oral administration. Following constitution, each 5 mL
 37 contains 100 mg of linezolid. Inactive ingredients are sucrose, citric acid, sodium citrate,
 38 microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum,
 39 mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors (see
 40 **PRECAUTIONS, Information for Patients**). The sodium (Na⁺) content is 8.52 mg per 5
 41 mL (0.4 mEq per 5 mL).
 42

43 **CLINICAL PHARMACOLOGY**

44 **Pharmacodynamics**

45 In a randomized, positive- and placebo-controlled crossover thorough QT study, 40 healthy
 46 subjects were administered a single ZYVOX 600 mg dose via a 1 hour IV infusion, a single
 47 ZYVOX 1200 mg dose via a 1 hour IV infusion, placebo, and a single oral dose of positive
 48 control. At both the 600 mg and 1200 mg ZYVOX doses, no significant effect on QTc
 49 interval was detected at peak plasma concentration or at any other time.
 50

51 **Pharmacokinetics**

52 The mean pharmacokinetic parameters of linezolid in adults after single and multiple oral
 53 and intravenous (IV) doses are summarized in Table 1. Plasma concentrations of linezolid
 54 at steady-state after oral doses of 600 mg given every 12 hours (q12h) are shown in Figure
 55 1.
 56

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

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-∞}; for multiple-dose = AUC_{0-τ}

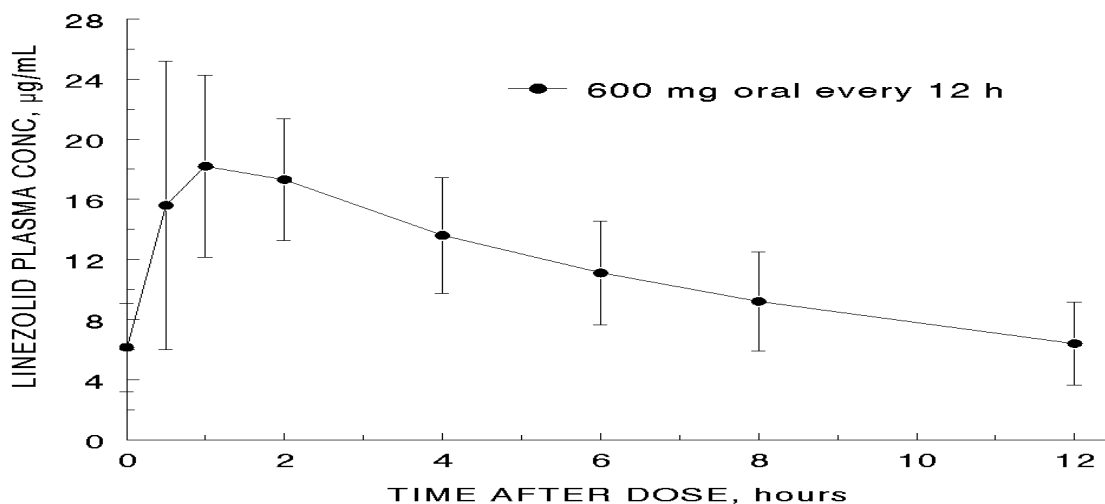
† Data dose-normalized from 375 mg

‡ 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

57



58

59

60 **Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-State Following Oral Dosing Every**
61 **12 Hours (Mean ± Standard Deviation, n=16)**

62

63

64 **Absorption:** Linezolid is rapidly and extensively absorbed after oral dosing. Maximum
65 plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute
66 bioavailability is approximately 100%. Therefore, linezolid may be given orally or
67 intravenously without dose adjustment.

68

69 Linezolid may be administered without regard to the timing of meals. The time to reach the
70 maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by
71 about 17% when high fat food is given with linezolid. However, the total exposure
72 measured as $AUC_{0-\infty}$ values is similar under both conditions.

73

74 **Distribution:** Animal and human pharmacokinetic studies have demonstrated that linezolid
75 readily distributes to well-perfused tissues. The plasma protein binding of linezolid is
76 approximately 31% and is concentration-independent. The volume of distribution of
77 linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers.

78

79 Linezolid concentrations have been determined in various fluids from a limited number of
80 subjects in Phase 1 volunteer studies following multiple dosing of linezolid. The ratio of
81 linezolid in saliva relative to plasma was 1.2 to 1 and for sweat relative to plasma was
82 0.55 to 1.

83

84 **Metabolism:** Linezolid is primarily metabolized by oxidation of the morpholine ring, which
85 results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid
86 metabolite (A), and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is
87 presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a
88 non-enzymatic chemical oxidation mechanism in vitro. In vitro studies have demonstrated

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

91

92 **Excretion:** Nonrenal clearance accounts for approximately 65% of the total clearance of
93 linezolid. Under steady-state conditions, approximately 30% of the dose appears in the
94 urine as linezolid, 40% as metabolite B, and 10% as metabolite A. The renal clearance of
95 linezolid is low (average 40 mL/min) and suggests net tubular reabsorption. Virtually no
96 linezolid appears in the feces, while approximately 6% of the dose appears in the feces as
97 metabolite B, and 3% as metabolite A.

98

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

103

104 **Special Populations**

105 **Geriatric:** The pharmacokinetics of linezolid are not significantly altered in elderly patients
106 (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

107

108 **Pediatric:** The pharmacokinetics of linezolid following a single IV dose were investigated
109 in pediatric patients ranging in age from birth through 17 years (including premature and
110 full-term neonates), in healthy adolescent subjects ranging in age from 12 through 17 years,
111 and in pediatric patients ranging in age from 1 week through 12 years. The
112 pharmacokinetic parameters of linezolid are summarized in Table 2 for the pediatric
113 populations studied and healthy adult subjects after administration of single IV doses.

114

115 The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age in
116 pediatric patients. However, clearance of linezolid varies as a function of age. With the
117 exclusion of pre-term neonates less than one week of age, clearance is most rapid in the
118 youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose
119 systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric
120 patients increases, the clearance of linezolid gradually decreases, and by adolescence mean
121 clearance values approach those observed for the adult population. There is wider inter-
122 subject variability in linezolid clearance and systemic drug exposure (AUC) across all
123 pediatric age groups as compared with adults.

124

125 Similar mean daily AUC values were observed in pediatric patients from birth to 11 years
126 of age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours
127 (q12h). Therefore, the dosage for pediatric patients up to 11 years of age should be 10
128 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h (see
129 **DOSAGE AND ADMINISTRATION**).

130

131

Table 2. 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} µg/mL	V _{ss} L/kg	AUC* µg•h/mL	t _{1/2} 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)†	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 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_{0-∞}

** 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

132

133 **Gender:** Females have a slightly lower volume of distribution of linezolid than males.
134 Plasma concentrations are higher in females than in males, which is partly due to body
135 weight differences. After a 600-mg dose, mean oral clearance is approximately 38% lower
136 in females than in males. However, there are no significant gender differences in mean
137 apparent elimination-rate constant or half-life. Thus, drug exposure in females is not
138 expected to substantially increase beyond levels known to be well tolerated. Therefore,
139 dose adjustment by gender does not appear to be necessary.

140

141 **Renal Insufficiency:** The pharmacokinetics of the parent drug, linezolid, are not altered in
142 patients with any degree of renal insufficiency; however, the two primary metabolites of
143 linezolid may accumulate in patients with renal insufficiency, with the amount of
144 accumulation increasing with the severity of renal dysfunction (see Table 3). The clinical
145 significance of accumulation of these two metabolites has not been determined in patients

146 with severe renal insufficiency. Because similar plasma concentrations of linezolid are
147 achieved regardless of renal function, no dose adjustment is recommended for patients with
148 renal insufficiency. However, given the absence of information on the clinical significance
149 of accumulation of the primary metabolites, use of linezolid in patients with renal
150 insufficiency should be weighed against the potential risks of accumulation of these
151 metabolites. Both linezolid and the two metabolites are eliminated by dialysis. No
152 information is available on the effect of peritoneal dialysis on the pharmacokinetics of
153 linezolid. Approximately 30% of a dose was eliminated in a 3-hour dialysis session
154 beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should
155 be given after hemodialysis.
156

Table 3. 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-∞} , 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

157
158 **Hepatic Insufficiency:** The pharmacokinetics of linezolid are not altered in patients (n=7)
159 with mild-to-moderate hepatic insufficiency (Child-Pugh class A or B). On the basis of the
160 available information, no dose adjustment is recommended for patients with mild-to-
161 moderate hepatic insufficiency. The pharmacokinetics of linezolid in patients with severe
162 hepatic insufficiency have not been evaluated.
163

164 **Drug-Drug Interactions**

165 **Drugs Metabolized by Cytochrome P450:** Linezolid is not an inducer of cytochrome P450
166 (CYP450) in rats. In addition, linezolid does not inhibit the activities of clinically
167 significant human CYP isoforms (e.g., 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore,
168 linezolid is not expected to affect the pharmacokinetics of other drugs metabolized by these
169 major enzymes. Concurrent administration of linezolid does not substantially alter the
170 pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by
171 CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be
172 given with linezolid without changes in dosage regimen.
173

174 **Antibiotics:**

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

177

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

180

181 *Rifampin:* The effect of rifampin on the pharmacokinetics of linezolid was evaluated in a
182 study of 16 healthy adult males. Volunteers were administered oral linezolid 600 mg twice
183 daily for 5 doses with and without rifampin 600 mg once daily for 8 days. Co-
184 administration of rifampin with linezolid resulted in a 21% decrease in linezolid C_{max} [90%
185 CI, 15% - 27%] and a 32% decrease in linezolid AUC_{0-12} [90% CI, 27% - 37%]. The
186 mechanism of this interaction is not fully understood and may be related to the induction of
187 hepatic enzymes (see **PRECAUTIONS, Drug Interactions**).

188

189 ***Monoamine Oxidase Inhibition:*** Linezolid is a reversible, nonselective inhibitor of
190 monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic
191 and serotonergic agents.

192

193 *Adrenergic Agents:* A significant pressor response has been observed in normal adult
194 subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients
195 receiving linezolid need to avoid consuming large amounts of foods or beverages with high
196 tyramine content (see **PRECAUTIONS, Information for Patients**).

197

198 A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or
199 phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy
200 normotensive subjects (see **PRECAUTIONS, Drug Interactions**). A similar study has not
201 been conducted in hypertensive patients. The interaction studies conducted in
202 normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA
203 or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg q12h
204 for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate
205 was not affected by any of the treatments. Blood pressure was increased with both
206 combination treatments. Maximum blood pressure levels were seen 2 to 3 hours after the
207 second dose of PPA or PSE, and returned to baseline 2 to 3 hours after peak. The results of
208 the PPA study follow, showing the mean (and range) maximum systolic blood pressure in
209 mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125
210 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were
211 similar to those in the PPA study. The mean maximum increase in systolic blood pressure
212 over baseline was 32 mm Hg (range: 20-52 mm Hg) and 38 mm Hg (range: 18-79 mm Hg)
213 during co-administration of linezolid with pseudoephedrine or phenylpropanolamine,
214 respectively.

215

216 *Serotonergic Agents:* The potential drug-drug interaction with dextromethorphan was
217 studied in healthy volunteers. Subjects were administered dextromethorphan (two 20-mg
218 doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects
219 (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been
220 observed in normal subjects receiving linezolid and dextromethorphan.

221 **MICROBIOLOGY**

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

233

234 In clinical trials, resistance to linezolid developed in 6 patients infected with *Enterococcus*
235 *faecium* (4 patients received 200 mg q12h, lower than the recommended dose, and 2
236 patients received 600 mg q12h). In a compassionate use program, resistance to linezolid
237 developed in 8 patients with *E. faecium* and in 1 patient with *Enterococcus faecalis*. All
238 patients had either unremoved prosthetic devices or undrained abscesses. Resistance to
239 linezolid occurs in vitro at a frequency of 1×10^{-9} to 1×10^{-11} . In vitro studies have
240 shown that point mutations in the 23S rRNA are associated with linezolid resistance.
241 Reports of vancomycin-resistant *E. faecium* becoming resistant to linezolid during its
242 clinical use have been published.¹ In one report nosocomial spread of vancomycin- and
243 linezolid-resistant *E. faecium* occurred.² There has been a report of *Staphylococcus aureus*
244 (methicillin-resistant) developing resistance to linezolid during its clinical use.³ The
245 linezolid resistance in these organisms was associated with a point mutation in the 23S
246 rRNA (substitution of thymine for guanine at position 2576) of the organism. When
247 antibiotic-resistant organisms are encountered in the hospital, it is important to emphasize
248 infection control policies.^{4,5} Resistance to linezolid has not been reported in *Streptococcus*
249 spp., including *Streptococcus pneumoniae*.

250

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

254

255 Linezolid has been shown to be active against most isolates of the following
256 microorganisms, both in vitro and in clinical infections, as described in the
257 **INDICATIONS AND USAGE** section.

258

259 **Aerobic and facultative Gram-positive microorganisms**

260 *Enterococcus faecium* (vancomycin-resistant strains only)

261 *Staphylococcus aureus* (including methicillin-resistant strains)

262 *Streptococcus agalactiae*

263 *Streptococcus pneumoniae* (including multi-drug resistant isolates [MDRSP]*)

264 *Streptococcus pyogenes*

265

266 The following in vitro data are available, but their clinical significance is unknown. At
267 least 90% of the following microorganisms exhibit an in vitro minimum inhibitory
268 concentration (MIC) less than or equal to the susceptible breakpoint for linezolid.

269 However, the safety and effectiveness of linezolid in treating clinical infections due to these
270 microorganisms have not been established in adequate and well-controlled clinical trials.

271

272 **Aerobic and facultative Gram-positive microorganisms**

273 *Enterococcus faecalis* (including vancomycin-resistant strains)

274 *Enterococcus faecium* (vancomycin-susceptible strains)

275 *Staphylococcus epidermidis* (including methicillin-resistant strains)

276 *Staphylococcus haemolyticus*

277 Viridans group streptococci

278

279 **Aerobic and facultative Gram-negative microorganisms**

280 *Pasteurella multocida*

281

282 **Susceptibility Testing Methods**

283 **NOTE:** Susceptibility testing by dilution methods requires the use of linezolid
284 susceptibility powder.

285

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

290

291 **Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimum
292 inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of
293 bacteria to antimicrobial compounds. The MICs should be determined using a standardized
294 procedure. Standardized procedures are based on a dilution method^{6,7} (broth or agar) or
295 equivalent with standardized inoculum concentrations and standardized concentrations of
296 linezolid powder. The MIC values should be interpreted according to criteria provided in
297 Table 4.

298

299 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters
300 also provide reproducible estimates of the susceptibility of bacteria to antimicrobial
301 compounds. One such standardized procedure^{7,8} requires the use of standardized inoculum

* MDRSP refers to isolates resistant to two or more of the following antibiotics:
penicillin, second-generation cephalosporins, macrolides, tetracycline, and
trimethoprim/sulfamethoxazole.

302 concentrations. This procedure uses paper disks impregnated with 30 µg of linezolid to test
 303 the susceptibility of microorganisms to linezolid. The disk diffusion interpretive criteria
 304 are provided in Table 4.
 305
 306

Table 4. Susceptibility Interpretive Criteria for Linezolid

Pathogen	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in µg/mL)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
<i>Enterococcus</i> spp	≤ 2	4	≥ 8	≥ 23	21-22	≤ 20
<i>Staphylococcus</i> spp ^a	≤ 4	---	---	≥ 21	---	---
<i>Streptococcus pneumoniae</i> ^a	≤ 2 ^b	---	---	≥ 21 ^c	---	---
<i>Streptococcus</i> spp other than <i>S. pneumoniae</i> ^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% CO₂ at 35°C for 20 to 24 hours.

307
 308 A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the
 309 antimicrobial compound in the blood reaches the concentrations usually achievable. A
 310 report of “Intermediate” indicates that the result should be considered equivocal, and, if the
 311 microorganism is not fully susceptible to alternative, clinically feasible drugs, the test
 312 should be repeated. This category implies possible clinical applicability in body sites
 313 where the drug is physiologically concentrated or in situations where high dosage of drug
 314 can be used. This category also provides a buffer zone which prevents small uncontrolled
 315 technical factors from causing major discrepancies in interpretation. A report of
 316 “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial
 317 compound in the blood reaches the concentrations usually achievable; other therapy should
 318 be selected.

319
 320 **Quality Control**

321 Standardized susceptibility test procedures require the use of quality control
 322 microorganisms to control the technical aspects of the test procedures. Standard linezolid
 323 powder should provide the following range of values noted in Table 5. **NOTE:** Quality
 324 control microorganisms are specific strains of organisms with intrinsic biological properties
 325 relating to resistance mechanisms and their genetic expression within bacteria; the specific
 326 strains used for microbiological quality control are not clinically significant.

327

Table 5. 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 µg/mL)	Disk Diffusion (Zone Diameters in mm)
<i>Enterococcus faecalis</i> ATCC 29212	1 - 4	Not applicable
<i>Staphylococcus aureus</i> ATCC 29213	1 - 4	Not applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not applicable	25 - 32
<i>Streptococcus pneumoniae</i> ATCC 49619 ^d	0.50 - 2 ^e	25 - 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% CO₂ at 35°C for 20 to 24 hours.

328

329

INDICATIONS AND USAGE

330

ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see **PRECAUTIONS**, **Pediatric Use** and **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES**). Linezolid is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see **WARNINGS**).

336

337

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

339

340

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]).

343

344

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers.

348

349

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

351

352 **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multi-
353 drug resistant strains [MDRSP]^{*}), including cases with concurrent bacteremia, or
354 *Staphylococcus aureus* (methicillin-susceptible strains only).
355

356 To reduce the development of drug-resistant bacteria and maintain the effectiveness of
357 ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent
358 infections that are proven or strongly suspected to be caused by susceptible bacteria. When
359 culture and susceptibility information are available, they should be considered in selecting
360 or modifying antibacterial therapy. In the absence of such data, local epidemiology and
361 susceptibility patterns may contribute to the empiric selection of therapy.
362

363 **CONTRAINDICATIONS**

364 ZYVOX formulations are contraindicated for use in patients who have known
365 hypersensitivity to linezolid or any of the other product components.
366

367 Monoamine Oxidase Inhibitors

368 Linezolid should not be used in patients taking any medicinal product which inhibits
369 monoamine oxidases A or B (e.g., phenelzine, isocarboxazid) or within two weeks of taking
370 any such medicinal product.
371

372 Potential Interactions Producing Elevation of Blood Pressure

373 Unless patients are monitored for potential increases in blood pressure, linezolid should not
374 be administered to patients with uncontrolled hypertension, pheochromocytoma,
375 thyrotoxicosis and/or patients taking any of the following types of medications: directly and
376 indirectly acting sympathomimetic agents (e.g., pseudoephedrine), vasopressive agents
377 (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine) (see
378 **PRECAUTIONS, Drug Interactions**).
379

380 Potential Serotonergic Interactions

381 Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome,
382 linezolid should not be administered to patients with carcinoid syndrome and/or patients
383 taking any of the following medications: serotonin re-uptake inhibitors, tricyclic
384 antidepressants, serotonin 5-HT₁ receptor agonists (triptans), meperidine or buspirone (see
385 **PRECAUTIONS, General and Drug Interactions**).
386

387 **WARNINGS**

388 **Myelosuppression (including anemia, leukopenia, pancytopenia, and**
389 **thrombocytopenia) has been reported in patients receiving linezolid. In cases where**
390 **the outcome is known, when linezolid was discontinued, the affected hematologic**
391 **parameters have risen toward pretreatment levels. Complete blood counts should be**
392 **monitored weekly in patients who receive linezolid, particularly in those who receive**
393 **linezolid for longer than two weeks, those with pre-existing myelosuppression, those**

* MDRSP refers to isolates resistant to two or more of the following antibiotics:
penicillin, second-generation cephalosporins, macrolides, tetracycline, and
trimethoprim/sulfamethoxazole.

394 **receiving concomitant drugs that produce bone marrow suppression, or those with a**
395 **chronic infection who have received previous or concomitant antibiotic therapy.**
396 **Discontinuation of therapy with linezolid should be considered in patients who**
397 **develop or have worsening myelosuppression.**

398
399 In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary
400 hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and
401 spleen were observed (see **ANIMAL PHARMACOLOGY**).

402
403 **Mortality Imbalance in an Investigational Study in Patients with Catheter-Related**
404 **Bloodstream Infections, including those with catheter-site infections**

405
406 An imbalance in mortality was seen in patients treated with linezolid relative to
407 vancomycin/dicloxacillin/oxacillin in an open-label study in seriously ill patients with
408 intravascular catheter-related infections [78/363 (21.5%) vs. 58/363 (16.0%); odds ratio
409 1.426, 95% CI 0.970, 2.098]. While causality has not been established, this observed
410 imbalance occurred primarily in linezolid-treated patients in whom either Gram-negative
411 pathogens, mixed Gram-negative and Gram-positive pathogens, or no pathogen were
412 identified at baseline, but was not seen in patients with Gram-positive infections only.

413
414 Linezolid is not approved and should not be used for the treatment of patients with catheter-
415 related bloodstream infections or catheter-site infections.

416
417 Linezolid has no clinical activity against Gram-negative pathogens and is not indicated for
418 the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy
419 be initiated immediately if a concomitant Gram-negative pathogen is documented or
420 suspected (see **INDICATIONS AND USAGE**).

421
422 *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all
423 antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to
424 fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading
425 to overgrowth of *C. difficile*.

426
427 *C. difficile* produces toxins A and B which contribute to the development of CDAD.
428 Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as
429 these infections can be refractory to antimicrobial therapy and may require colectomy.
430 CDAD must be considered in all patients who present with diarrhea following antibiotic
431 use.

432
433 Careful medical history is necessary since CDAD has been reported to occur over two
434 months after the administration of antibacterial agents.

435
436 If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile*
437 may need to be discontinued. Appropriate fluid and electrolyte management, protein
438 supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be
439 instituted as clinically indicated.

440

441 **Hypoglycemia**

442 Postmarketing cases of symptomatic hypoglycemia have been reported in patients with diabetes
443 mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid, a reversible,
444 nonselective MAO inhibitor. Some MAO inhibitors have been associated with hypoglycemic
445 episodes in diabetic patients receiving insulin or hypoglycemic agents. While a causal relationship
446 between linezolid and hypoglycemia has not been established, diabetic patients should be cautioned
447 of potential hypoglycemic reactions when treated with linezolid.

448 If hypoglycemia occurs, a decrease in the dose of insulin or oral hypoglycemic agent, or
449 discontinuation of oral hypoglycemic agent, insulin, or linezolid may be required.

450

451 **PRECAUTIONS**

452 **General**

453 **Lactic Acidosis**

454 **Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients**
455 **experienced repeated episodes of nausea and vomiting. Patients who develop**
456 **recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while**
457 **receiving ZYVOX should receive immediate medical evaluation.**

458

459 **Serotonin Syndrome**

460 **Spontaneous reports of serotonin syndrome associated with the co-administration of**
461 **ZYVOX and serotonergic agents, including antidepressants such as selective serotonin**
462 **reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug**
463 **Interactions).**

464

465 **Where administration of ZYVOX and concomitant serotonergic agents is clinically**
466 **appropriate, patients should be closely observed for signs and symptoms of serotonin**
467 **syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and**
468 **incoordination. If signs or symptoms occur physicians should consider discontinuation**
469 **of either one or both agents. If the concomitant serotonergic agent is withdrawn,**
470 **discontinuation symptoms can be observed (see package insert of the specified**
471 **agent(s) for a description of the associated discontinuation symptoms).**

472

473 **Peripheral and Optic Neuropathy**

474 **Peripheral and optic neuropathy have been reported in patients treated with ZYVOX,**
475 **primarily those patients treated for longer than the maximum recommended duration of 28**
476 **days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for**
477 **extended periods beyond the maximum recommended duration. Visual blurring has been**
478 **reported in some patients treated with ZYVOX for less than 28 days.**

479

480 **If patients experience symptoms of visual impairment, such as changes in visual acuity,**
481 **changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation**
482 **is recommended. Visual function should be monitored in all patients taking ZYVOX**
483 **for extended periods (≥ 3 months) and in all patients reporting new visual symptoms**
484 **regardless of length of therapy with ZYVOX. If peripheral or optic neuropathy occurs,**
485 **the continued use of ZYVOX in these patients should be weighed against the potential**
486 **risks.**

487

488

489 **Convulsions**

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

492

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

495

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

498

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

501

502 Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or
503 a prophylactic indication is unlikely to provide benefit to the patient and increases the risk
504 of the development of drug-resistant bacteria.

505

506 **Information for Patients**

507 Patients should be advised that:

508

- 508 • ZYVOX may be taken with or without food.
- 509 • They should inform their physician if they have a history of hypertension.
- 510 • Large quantities of foods or beverages with high tyramine content should be avoided
511 while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg
512 per meal. Foods high in tyramine content include those that may have undergone
513 protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as
514 aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to
515 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce
516 (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines
517 (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may
518 be increased if stored for long periods or improperly refrigerated.^{9,10}
- 519 • They should inform their physician if taking medications containing pseudoephedrine
520 HCl or phenylpropanolamine HCl, such as cold remedies and decongestants.
- 521 • They should inform their physician if taking serotonin re-uptake inhibitors or other
522 antidepressants.
- 523 • *Phenylketonurics*: Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension
524 contains 20 mg phenylalanine. The other ZYVOX formulations do not contain
525 phenylalanine. Contact your physician or pharmacist.
- 526 • They should inform their physician if they experience changes in vision.
- 527 • They should inform their physician if they have a history of seizures.
- 528 • Diarrhea is a common problem caused by antibiotics, which usually ends when the
529 antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients
530 can develop watery and bloody stools (with or without stomach cramps and fever) even
531 as late as two or more months after having taken the last dose of the antibiotic. If this
532 occurs, patients should contact their physician as soon as possible.

533

534 Patients should be counseled that antibacterial drugs including ZYVOX should only be
535 used to treat bacterial infections. They do not treat viral infections (e.g., the common cold).

536 When ZYVOX is prescribed to treat a bacterial infection, patients should be told that
537 although it is common to feel better early in the course of therapy, the medication should be
538 taken exactly as directed. Skipping doses or not completing the full course of therapy may
539 (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood
540 that bacteria will develop resistance and will not be treatable by ZYVOX or other
541 antibacterial drugs in the future.
542

543 **Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug-Drug Interactions)**
544 **Monoamine Oxidase Inhibition:** Linezolid is a reversible, nonselective inhibitor of
545 monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic
546 and serotonergic agents.
547
548 **Adrenergic Agents:** Some individuals receiving ZYVOX may experience a reversible
549 enhancement of the pressor response to indirect-acting sympathomimetic agents,
550 vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine
551 and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents,
552 such as dopamine or epinephrine, should be reduced and titrated to achieve the desired
553 response.
554
555 **Serotonergic Agents:** Co-administration of linezolid and serotonergic agents was not
556 associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of
557 serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents,
558 including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been
559 reported. Patients who are treated with ZYVOX and concomitant serotonergic agents
560 should be closely observed as described in the PRECAUTIONS, General Section.
561
562 **Strong CYP450 Inducers:** In a study in healthy volunteers, co-administration of rifampin
563 with oral linezolid resulted in a 21% decrease in linezolid C_{max} and a 32% decrease in
564 linezolid AUC_{0-12} . The clinical significance of this interaction is unknown. Other strong
565 inducers of hepatic enzymes (e.g. carbamazepine, phenytoin, phenobarbital) could cause a
566 similar or smaller decrease in linezolid exposure (see **CLINICAL PHARMACOLOGY,**
567 **Drug-Drug Interactions**)
568
569 **Drug-Laboratory Test Interactions**
570 There are no reported drug-laboratory test interactions.
571
572 **Carcinogenesis, Mutagenesis, Impairment of Fertility**
573 Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential
574 of linezolid. Neither mutagenic nor clastogenic potential was found in a battery of tests
575 including: assays for mutagenicity (Ames bacterial reversion and CHO cell mutation), an in
576 vitro unscheduled DNA synthesis (UDS) assay, an in vitro chromosome aberration assay in
577 human lymphocytes, and an in vivo mouse micronucleus assay.
578
579 Linezolid did not affect the fertility or reproductive performance of adult female rats. It
580 reversibly decreased fertility and reproductive performance in adult male rats when given at
581 doses ≥ 50 mg/kg/day, with exposures approximately equal to or greater than the expected
582 human exposure level (exposure comparisons are based on AUCs). The reversible fertility
583 effects were mediated through altered spermatogenesis. Affected spermatids contained
584 abnormally formed and oriented mitochondria and were non-viable. Epithelial cell
585 hypertrophy and hyperplasia in the epididymis was observed in conjunction with decreased
586 fertility. Similar epididymal changes were not seen in dogs.
587
588 In sexually mature male rats exposed to drug as juveniles, mildly decreased fertility was
589 observed following treatment with linezolid through most of their period of sexual

590 development (50 mg/kg/day from days 7 to 36 of age, and 100 mg/kg/day from days 37 to
591 55 of age), with exposures up to 1.7-fold greater than mean AUCs observed in pediatric
592 patients aged 3 months to 11 years. Decreased fertility was not observed with shorter
593 treatment periods, corresponding to exposure in utero through the early neonatal period
594 (gestation day 6 through postnatal day 5), neonatal exposure (postnatal days 5 to 21), or to
595 juvenile exposure (postnatal days 22 to 35). Reversible reductions in sperm motility and
596 altered sperm morphology were observed in rats treated from postnatal day 22 to 35.

597

598 **Pregnancy**

599 **Teratogenic Effects. Pregnancy Category C:** Linezolid was not teratogenic in mice, rats,
600 or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.06-fold (in
601 rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal
602 toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-
603 controlled studies in pregnant women. ZYVOX should be used during pregnancy only if
604 the potential benefit justifies the potential risk to the fetus.

605

606 **Non-teratogenic Effects**

607 In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity
608 (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the
609 estimated human exposure level based on AUCs) correlated with increased
610 postimplantational embryo death, including total litter loss, decreased fetal body weights,
611 and an increased incidence of costal cartilage fusion.

612

613 In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold
614 to approximately equivalent to the estimated human exposure, respectively based on
615 AUCs). The effects consisted of decreased fetal body weights and reduced ossification of
616 sternebrae, a finding often seen in association with decreased fetal body weights. Slight
617 maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day.

618

619 In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity
620 (clinical signs, reduced body weight gain and food consumption) when administered at a
621 dose of 15 mg/kg/day (0.06-fold the estimated human exposure based on AUCs).

622

623 When female rats were treated with 50 mg/kg/day (approximately equivalent to the
624 estimated human exposure based on AUCs) of linezolid during pregnancy and lactation,
625 survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted
626 to mature to reproductive age, when mated, showed an increase in preimplantation loss.

627

628 **Nursing Mothers**

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

633

634 **Pediatric Use**

635 The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the
636 following infections are supported by evidence from adequate and well-controlled studies

637 in
638 adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-
639 controlled study of Gram-positive infections in pediatric patients ranging in age from birth
640 through 11 years (see **INDICATIONS AND USAGE** and **CLINICAL STUDIES**):

- 641 • nosocomial pneumonia
- 642 • complicated skin and skin structure infections
- 643 • community-acquired pneumonia (also supported by evidence from an uncontrolled
644 study in patients ranging in age from 8 months through 12 years)
- 645 • vancomycin-resistant *Enterococcus faecium* infections

646
647 The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the
648 following infection have been established in a comparator-controlled study in pediatric
649 patients ranging in age from 5 through 17 years (see **CLINICAL STUDIES**):

- 650 • uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*
651 (methicillin-susceptible strains only) or *Streptococcus pyogenes*

652
653 Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal
654 shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single
655 and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved
656 or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of
657 pediatric patients with central nervous system infections is not recommended.

658
659 The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age in
660 pediatric patients. However, linezolid clearance is a function of age. Excluding neonates
661 less than a week of age, clearance is most rapid in the youngest age groups ranging from >1
662 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter
663 half-life as compared with adults. As age of pediatric patients increases, the clearance of
664 linezolid gradually decreases, and by adolescence, mean clearance values approach those
665 observed for the adult population. There is wider inter-subject variability in linezolid
666 clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared
667 with adults.

668 Similar mean daily AUC values were observed in pediatric patients from birth to 11 years
669 of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for
670 pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years
671 and older should receive 600 mg q12h.

672
673 Recommendations for the dosage regimen for pre-term neonates less than 7 days of age
674 (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term
675 neonates. Most of these pre-term neonates have lower systemic linezolid clearance values
676 and larger AUC values than many full-term neonates and older infants. Therefore, these
677 pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h.
678 Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-
679 optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of
680 life (see **CLINICAL PHARMACOLOGY, Special Populations, Pediatric** and
681 **DOSAGE AND ADMINISTRATION**).

682

683 In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to
684 Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures.
685 However, pediatric patients exhibit wider variability in linezolid clearance and systemic
686 exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical
687 response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic
688 exposure, site and severity of infection, and the underlying medical condition should be
689 considered when assessing clinical response (see **CLINICAL PHARMACOLOGY**,
690 **Special Populations, Pediatric** and **DOSAGE AND ADMINISTRATION**).

691

692 **Geriatric Use**

693 Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials,
694 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall
695 differences in safety or effectiveness were observed between these patients and younger
696 patients.

697

698 **ANIMAL PHARMACOLOGY**

699 Target organs of linezolid toxicity were similar in juvenile and adult rats and dogs. Dose-
700 and time-dependent myelosuppression, as evidenced by bone marrow
701 hypocellularity/decreased hematopoiesis, decreased extramedullary hematopoiesis in spleen
702 and liver, and decreased levels of circulating erythrocytes, leukocytes, and platelets have
703 been seen in animal studies. Lymphoid depletion occurred in thymus, lymph nodes, and
704 spleen. Generally, the lymphoid findings were associated with anorexia, weight loss, and
705 suppression of body weight gain, which may have contributed to the observed effects.

706

707 In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal
708 degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the
709 sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy.
710 Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate
711 evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was
712 evident in 2 male rats after 6 months of dosing, but the direct relationship to drug was
713 equivocal because of the acute nature of the finding and its asymmetrical distribution. The
714 nerve degeneration observed was microscopically comparable to spontaneous unilateral
715 optic nerve degeneration reported in aging rats and may be an exacerbation of common
716 background change.

717

718 These effects were observed at exposure levels that are comparable to those observed in
719 some human subjects. The hematopoietic and lymphoid effects were reversible, although in
720 some studies, reversal was incomplete within the duration of the recovery period.

721

722 **ADVERSE REACTIONS**

723 **Adult Patients**

724 The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven
725 Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these
726 studies, 85% of the adverse events reported with ZYVOX were described as mild to
727 moderate in intensity. Table 6 shows the incidence of adverse events reported in at least
728 2% of patients in these trials. The most common adverse events in patients treated with
729 ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence
730 across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%).

731
732

**Table 6. Incidence (%) of Adverse Events Reported in \geq 2% of Adult 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.

733

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

737

738 Table 7 shows the incidence of drug-related adverse events reported in at least 1% of adult
739 patients in these trials by dose of ZYVOX.

740

Table 7. Incidence (%) of Drug-Related Adverse Events Occurring in >1% of Adult 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.

741

742

Pediatric Patients

743

The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. Table 8 shows the incidence of adverse events reported in at least 2% of pediatric patients treated with ZYVOX in these trials.

754

Table 8. Incidence (%) of Adverse Events Reported in $\geq 2\%$ of Pediatric Patients Treated with ZYVOX in Comparator-Controlled Clinical Trials

Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications [†]	
	ZYVOX (n=248)	Cefadroxil (n = 251)	ZYVOX (n = 215)	Vancomycin (n=101)
Fever	2.9	3.6	14.1	14.1
Diarrhea	7.8	8.0	10.8	12.1
Vomiting	2.9	6.4	9.4	9.1
Sepsis	0	0	8.0	7.1
Rash	1.6	1.2	7.0	15.2
Headache	6.5	4.0	0.9	0
Anemia	0	0	5.6	7.1
Thrombocytopenia	0	0	4.7	2.0
Upper respiratory infection	3.7	5.2	4.2	1.0
Nausea	3.7	3.2	1.9	0
Dyspnea	0	0	3.3	1.0
Reaction at site of injection or of vascular catheter	0	0	3.3	5.1
Trauma	3.3	4.8	2.8	2.0
Pharyngitis	2.9	1.6	0.5	1.0
Convulsion	0	0	2.8	2.0
Hypokalemia	0	0	2.8	3.0
Pneumonia	0	0	2.8	2.0
Thrombocythemia	0	0	2.8	2.0
Cough	2.4	4.0	0.9	0
Generalized abdominal pain	2.4	2.8	0.9	2.0
Localized abdominal pain	2.4	2.8	0.5	1.0
Apnea	0	0	2.3	2.0
Gastrointestinal bleeding	0	0	2.3	1.0
Generalized edema	0	0	2.3	1.0
Loose stools	1.6	0.8	2.3	3.0
Localized pain	2.0	1.6	0.9	0
Skin disorder	2.0	0	0.9	1.0

* Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

[†] Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

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Table 9 shows the incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

Table 9. Incidence (%) of Drug-related Adverse Events Occurring in >1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-Controlled Clinical Trials

Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications [†]	
	ZYVOX (n=248)	Cefadroxil (n=251)	ZYVOX (n=215)	Vancomycin (n=101)
% of patients with ≥1 drug-related adverse event	19.2	14.1	18.8	34.3
% of patients discontinuing due to a drug-related adverse event	1.6	2.4	0.9	6.1
Diarrhea	5.7	5.2	3.8	6.1
Nausea	3.3	2.0	1.4	0
Headache	2.4	0.8	0	0
Loose stools	1.2	0.8	1.9	0
Thrombocytopenia	0	0	1.9	0
Vomiting	1.2	2.4	1.9	1.0
Generalized abdominal pain	1.6	1.2	0	0
Localized abdominal pain	1.6	1.2	0	0
Anemia	0	0	1.4	1.0
Eosinophilia	0.4	0.4	1.4	0
Rash	0.4	1.2	1.4	7.1
Vertigo	1.2	0.4	0	0
Oral moniliasis	0	0	0.9	4.0
Fever	0	0	0.5	3.0
Pruritus at non-application site	0.4	0	0	2.0
Anaphylaxis	0	0	0	10.1 [‡]

* Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

[†] Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

[‡] These reports were of ‘red-man syndrome’, which were coded as anaphylaxis.

761

762 **Laboratory Changes**

763 ZYVOX has been associated with thrombocytopenia when used in doses up to and
764 including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled
765 trials, the percentage of adult patients who developed a substantially low platelet count
766 (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among
767 studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a
768 comparator. In a study of hospitalized pediatric patients ranging in age from birth through
769 11 years, the percentage of patients who developed a substantially low platelet count
770 (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with
771 ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged
772 from 5 through 17 years, the percentage of patients who developed a substantially low
773 platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia
774 associated with the use of ZYVOX appears to be dependent on duration of therapy,
775 (generally greater than 2 weeks of treatment). The platelet counts for most patients
776 returned to the normal range/baseline during the follow-up period. No related clinical
777 adverse events were identified in Phase 3 clinical trials in patients developing
778 thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a

779 compassionate use program for ZYVOX; the role of linezolid in these events cannot be
780 determined (see **WARNINGS**).

781

782 Changes seen in other laboratory parameters, without regard to drug relationship, revealed
783 no substantial differences between ZYVOX and the comparators. These changes were
784 generally not clinically significant, did not lead to discontinuation of therapy, and were
785 reversible. The incidence of adult and pediatric patients with at least one substantially
786 abnormal hematologic or serum chemistry value is presented in Tables 10, 11, 12, and 13.
787

Table 10. Percent of Adult 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.

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Table 11. Percent of Adult 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.

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Table 12. Percent of Pediatric 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	Cefadroxil	ZYVOX	Vancomycin
Hemoglobin (g/dL)	0.0	0.0	15.7	12.4
Platelet count (x 10 ³ /mm ³)	0.0	0.4	12.9	13.4
WBC (x 10 ³ /mm ³)	0.8	0.8	12.4	10.3
Neutrophils (x 10 ³ /mm ³)	1.2	0.8	5.9	4.3

- * <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 ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.
- [‡] Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

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Table 13. Percent of Pediatric 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	Cefadroxil	ZYVOX	Vancomycin
ALT (U/L)	0.0	0.0	10.1	12.5
Lipase (U/L)	0.4	1.2	---	---
Amylase (U/L)	---	---	0.6	1.3
Total bilirubin (mg/dL)	---	---	6.3	5.2
Creatinine (mg/dL)	0.4	0.0	2.4	1.0

- * >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 ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.
- [‡] Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

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Postmarketing Experience

796 Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia)
797 has been reported during postmarketing use of ZYVOX (see **WARNINGS**). Peripheral
798 neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been
799 reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of
800 ZYVOX (see **PRECAUTIONS, General**). Although these reports have primarily been in
801 patients treated for longer than the maximum recommended duration of 28 days, these
802 events have also been reported in patients receiving shorter courses of therapy. Serotonin
803 syndrome has been reported in patients receiving concomitant serotonergic agents,
804 including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and
805 ZYVOX (see **PRECAUTIONS, General**). Convulsions have been reported with the use of
806 ZYVOX (see **PRECAUTIONS, General**). Anaphylaxis, angioedema, and bullous skin

807 disorders such as those described as Stevens Johnson syndrome have been reported.
808 Superficial tooth discoloration and tongue discoloration have been reported with the use of
809 linezolid. The tooth discoloration was removable with professional dental cleaning (manual
810 descaling) in cases with known outcome. Hypoglycemia, including symptomatic episodes,
811 has been reported (see WARNINGS). These events have been chosen for inclusion due to
812 either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a
813 combination of these factors. Because they are reported voluntarily from a population of
814 unknown size, estimates of frequency cannot be made and causal relationship cannot be
815 precisely established.

816

817 **OVERDOSAGE**

818 In the event of overdose, supportive care is advised, with maintenance of glomerular
819 filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1
820 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour
821 hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data
822 are not available for removal of linezolid with peritoneal dialysis or hemoperfusion.
823 Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and
824 vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day,
825 respectively.

826

827 **DOSAGE AND ADMINISTRATION**

828 The recommended dosage for ZYVOX formulations for the treatment of infections is
829 described in Table 14.

830

Table 14. Dosage Guidelines for ZYVOX

Infection*	Dosage and Route of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients† (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Complicated skin and skin structure infections	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	10 to 14
Community-acquired pneumonia, including concurrent bacteremia			
Nosocomial pneumonia			
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	14 to 28
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral‡ q8h 5-11 yrs: 10 mg/kg oral‡ q12h	Adults: 400 mg oral‡ q12h Adolescents: 600 mg oral‡ q12h	10 to 14

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

† **Neonates <7 days:** Most pre-term neonates < 7 days of age (gestational age < 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 q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life (see **CLINICAL PHARMACOLOGY, Special Populations, Pediatric**).

‡ Oral dosing using either ZYVOX Tablets or ZYVOX for Oral Suspension

831

832 Adult patients with infection due to MRSA should be treated with ZYVOX 600 mg q12h.

833

834 In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to
835 Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures.
836 However, pediatric patients exhibit wider variability in linezolid clearance and systemic
837 exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical
838 response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure,
839 site and severity of infection, and the underlying medical condition should be considered when
840 assessing clinical response (see **CLINICAL PHARMACOLOGY, Special Populations,**
841 **Pediatric** and **PRECAUTIONS, Pediatric Use**).

842

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

846

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

851

852

853 **Intravenous Administration**

854 ZYVOX I.V. Injection is supplied in single-use, ready-to-use infusion bags (see **HOW**
855 **SUPPLIED** for container sizes). Parenteral drug products should be inspected visually for
856 particulate matter prior to administration. Check for minute leaks by firmly squeezing the
857 bag. If leaks are detected, discard the solution, as sterility may be impaired.

858

859 ZYVOX I.V. Injection should be administered by intravenous infusion over a period of 30
860 to 120 minutes. **Do not use this intravenous infusion bag in series connections.**

861 Additives should not be introduced into this solution. If ZYVOX I.V. Injection is to be
862 given concomitantly with another drug, each drug should be given separately in accordance
863 with the recommended dosage and route of administration for each product. In particular,
864 physical incompatibilities resulted when ZYVOX I.V. Injection was combined with the
865 following drugs during simulated Y-site administration: amphotericin B, chlorpromazine
866 HCl, diazepam, pentamidine isothionate, erythromycin lactobionate, phenytoin sodium, and
867 trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when
868 ZYVOX I.V. Injection was combined with ceftriaxone sodium.

869

870 If the same intravenous line is used for sequential infusion of several drugs, the line should
871 be flushed before and after infusion of ZYVOX I.V. Injection with an infusion solution
872 compatible with ZYVOX I.V. Injection and with any other drug(s) administered via this
873 common line (see **Compatible Intravenous Solutions**).

874

875 **Compatible Intravenous Solutions**

876 5% Dextrose Injection, USP

877 0.9% Sodium Chloride Injection, USP

878 Lactated Ringer's Injection, USP

879

880 Keep the infusion bags in the overwrap until ready to use. Store at room temperature.

881 Protect from freezing. ZYVOX I.V. Injection may exhibit a yellow color that can intensify
882 over time without adversely affecting potency.

883

884 **Constitution of Oral Suspension**

885 ZYVOX for Oral Suspension is supplied as a powder/granule for constitution. Gently tap
886 bottle to loosen powder. Add a total of 123 mL distilled water in two portions. After
887 adding the first half, shake vigorously to wet all of the powder. Then add the second half of
888 the water and shake vigorously to obtain a uniform suspension. After constitution, each 5
889 mL of the suspension contains 100 mg of linezolid. Before using, gently mix by inverting
890 the bottle 3 to 5 times. **DO NOT SHAKE.** Store constituted suspension at room
891 temperature. Use within 21 days after constitution.

892

893 **HOW SUPPLIED**

894 **Injection**

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

898

899 100 mL bag (200 mg linezolid) NDC 0009-5137-01

900 200 mL bag (400 mg linezolid) NDC 0009-5139-01
901 300 mL bag (600 mg linezolid) NDC 0009-5140-01

902

903 **Tablets**

904 ZYVOX Tablets are available as follows:

905

906 **400 mg** (white, oblong, film-coated tablets printed with “ZYVOX 400mg”)

907 100 tablets in HDPE bottle NDC 0009-5134-01

908 20 tablets in HDPE bottle NDC 0009-5134-02

909 Unit dose packages of 30 tablets NDC 0009-5134-03

910

911 **600 mg** (white, capsule-shaped, film-coated tablets printed with “ZYVOX 600 mg”)

912 100 tablets in HDPE bottle NDC 0009-5135-01

913 20 tablets in HDPE bottle NDC 0009-5135-02

914 Unit dose packages of 30 tablets NDC 0009-5135-03

915

916 **Oral Suspension**

917 ZYVOX for Oral Suspension is available as a dry, white to off-white, orange-flavored
918 granule/powder. When constituted as directed, each bottle will contain 150 mL of a
919 suspension providing the equivalent of 100 mg of linezolid per each 5 mL. ZYVOX for
920 Oral Suspension is supplied as follows:

921

922 100 mg/5 mL in 240-mL glass bottles NDC 0009-5136-01

923

924 **Storage of ZYVOX Formulations**

925 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room
926 Temperature]. Protect from light. Keep bottles tightly closed to protect from moisture. It
927 is recommended that the infusion bags be kept in the overwrap until ready to use. Protect
928 infusion bags from freezing.

929

930 **CLINICAL STUDIES**

931

932 **Adults**

933 **Vancomycin-Resistant Enterococcal Infections**

934 Adult patients with documented or suspected vancomycin-resistant enterococcal infection
935 were enrolled in a randomized, multi-center, double-blind trial comparing a high dose of
936 ZYVOX (600 mg) with a low dose of ZYVOX (200 mg) given every 12 hours (q12h) either
937 intravenously (IV) or orally for 7 to 28 days. Patients could receive concomitant aztreonam
938 or aminoglycosides. There were 79 patients randomized to high-dose linezolid and 66 to
939 low-dose linezolid. The intent-to-treat (ITT) population with documented vancomycin-
940 resistant enterococcal infection at baseline consisted of 65 patients in the high-dose arm and
941 52 in the low-dose arm.

942

943 The cure rates for the ITT population with documented vancomycin-resistant enterococcal
944 infection at baseline are presented in Table 15 by source of infection. These cure rates do
945 not include patients with missing or indeterminate outcomes. The cure rate was higher in

946 the high-dose arm than in the low-dose arm, although the difference was not statistically
947 significant at the 0.05 level.
948

Table 15. Cure Rates at the Test-of-Cure Visit for ITT Adult 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, pericolic abscess, pancreatitis, and catheter-related infection.

949

950 Nosocomial Pneumonia

951 Adult patients with clinically and radiologically documented nosocomial pneumonia were
952 enrolled in a randomized, multi-center, double-blind trial. Patients were treated for 7 to 21
953 days. One group received ZYVOX I.V. Injection 600 mg q12h, and the other group
954 received vancomycin 1 g q12h IV. Both groups received concomitant aztreonam (1 to 2 g
955 every 8 hours IV), which could be continued if clinically indicated. There were 203
956 linezolid-treated and 193 vancomycin-treated patients enrolled in the study. One hundred
957 twenty-two (60%) linezolid-treated patients and 103 (53%) vancomycin-treated patients
958 were clinically evaluable. The cure rates in clinically evaluable patients were 57% for
959 linezolid-treated patients and 60% for vancomycin-treated patients. The cure rates in
960 clinically evaluable patients with ventilator-associated pneumonia were 47% for linezolid-
961 treated patients and 40% for vancomycin-treated patients. A modified intent-to-treat
962 (MITT) analysis of 94 linezolid-treated patients and 83 vancomycin-treated patients
963 included subjects who had a pathogen isolated before treatment. The cure rates in the
964 MITT analysis were 57% in linezolid-treated patients and 46% in vancomycin-treated
965 patients. The cure rates by pathogen for microbiologically evaluable patients are presented
966 in Table 16.

967

Table 16. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Nosocomial Pneumonia

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

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Pneumonia caused by multi-drug resistant *S.pneumoniae* (MDRSP*)

ZYVOX was studied for the treatment of community-acquired (CAP) and hospital-acquired (HAP) pneumonia due to MDRSP by pooling clinical data from seven comparative and non-comparative Phase 2 and Phase 3 studies involving adult and pediatric patients. The pooled MITT population consisted of all patients with *S.pneumoniae* isolated at baseline; the pooled ME population consisted of patients satisfying criteria for microbiologic evaluability. The pooled MITT population with CAP included 15 patients (41%) with severe illness (risk classes IV and V) as assessed by a prediction rule¹¹. The pooled clinical cure rates for patients with CAP due to MDRSP were 35/48 (73%) in the MITT and 33/36 (92%) in the ME populations respectively. The pooled clinical cure rates for patients with HAP due to MDRSP were 12/18 (67%) in the MITT and 10/12 (83%) in the ME populations respectively.

Table 17. Clinical cure rates for 36 microbiologically-evaluable patients with CAP due to MDRSP* who were treated with ZYVOX (stratified by antibiotic susceptibility)

Susceptibility Screening	Clinical Cure	
	n/N ^a	(%)
Penicillin-resistant	14/16	88
2 nd generation cephalosporin-resistant ^b	19/22	86
Macrolide-resistant ^c	29/30	97
Tetracycline-resistant	22/24	92
Trimethoprim/sulfamethoxazole-resistant	18/21	86

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- a) n= pooled number of patients treated successfully; N= pooled number of patients having MDRSP isolates that exhibited resistance to the listed antibiotic
- b) 2nd-generation cephalosporin tested was cefuroxime
- c) macrolide tested was erythromycin

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

* MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

1001 study entry. The cure rates in the MITT analysis were 86% in linezolid-treated patients and
1002 82% in oxacillin-treated patients. The cure rates by pathogen for microbiologically
1003 evaluable patients are presented in Table 18.
1004
1005

**Table 18. Cure Rates at the Test-of-Cure Visit for Microbiologically
Evaluable Adult Patients with Complicated Skin and Skin Structure Infections**

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

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1008 A separate study provided additional experience with the use of ZYVOX in the treatment of
1009 methicillin-resistant *Staphylococcus aureus* (MRSA) infections. This was a randomized,
1010 open-label trial in hospitalized adult patients with documented or suspected MRSA
1011 infection.

1012

1013 One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX
1014 Tablets 600 mg q12h. The other group of patients received vancomycin 1 g q12h IV. Both
1015 groups were treated for 7 to 28 days, and could receive concomitant aztreonam or
1016 gentamicin if clinically indicated. The cure rates in microbiologically evaluable patients
1017 with MRSA skin and skin structure infection were 26/33 (79%) for linezolid-treated
1018 patients and 24/33 (73%) for vancomycin-treated patients.

1019

1020 **Diabetic Foot Infections**

1021 Adult diabetic patients with clinically documented complicated skin and skin structure
1022 infections (“diabetic foot infections”) were enrolled in a randomized (2:1 ratio), multi-
1023 center, open-label trial comparing study medications administered IV or orally for a total of
1024 14 to 28 days of treatment. One group of patients received ZYVOX 600 mg q12h IV or
1025 orally; the other group received ampicillin/sulbactam 1.5 to 3 g IV or
1026 amoxicillin/clavulanate 500 to 875 mg every 8 to 12 hours (q8-12h) orally. In countries
1027 where ampicillin/sulbactam is not marketed, amoxicillin/clavulanate 500 mg to 2 g every 6
1028 hours (q6h) was used for the intravenous regimen. Patients in the comparator group could
1029 also be treated with vancomycin 1 g q12h IV if MRSA was isolated from the foot infection.
1030 Patients in either treatment group who had Gram-negative bacilli isolated from the infection
1031 site could also receive aztreonam 1 to 2 g q8-12h IV. All patients were eligible to receive
1032 appropriate adjunctive treatment methods, such as debridement and off-loading, as typically
1033 required in the treatment of diabetic foot infections, and most patients received these
1034 treatments. There were 241 linezolid-treated and 120 comparator-treated patients in the
1035 intent-to-treat (ITT) study population. Two hundred twelve (86%) linezolid-treated
1036 patients and 105 (85%) comparator-treated patients were clinically evaluable. In the ITT
1037 population, the cure rates were 68.5% (165/241) in linezolid-treated patients and 64%
1038 (77/120) in comparator-treated patients, where those with indeterminate and missing

1039 outcomes were considered failures. The cure rates in the clinically evaluable patients
 1040 (excluding those with indeterminate and missing outcomes) were 83% (159/192) and 73%
 1041 (74/101) in the linezolid- and comparator-treated patients, respectively. A critical post-hoc
 1042 analysis focused on 121 linezolid-treated and 60 comparator-treated patients who had a
 1043 Gram-positive pathogen isolated from the site of infection or from blood, who had less
 1044 evidence of underlying osteomyelitis than the overall study population, and who did not
 1045 receive prohibited antimicrobials. Based upon that analysis, the cure rates were 71%
 1046 (86/121) in the linezolid-treated patients and 63% (38/60) in the comparator-treated
 1047 patients. None of the above analyses were adjusted for the use of adjunctive therapies. The
 1048 cure rates by pathogen for microbiologically evaluable patients are presented in Table 19.
 1049

**Table 19. Cure Rates at the Test-of-Cure Visit for Microbiologically
 Evaluable Adult Patients with Diabetic Foot Infections**

Pathogen	Cured	
	ZYVOX n/N (%)	Comparator n/N (%)
<i>Staphylococcus aureus</i>	49/63 (78)	20/29 (69)
Methicillin-resistant <i>S. aureus</i>	12/17 (71)	2/3 (67)
<i>Streptococcus agalactiae</i>	25/29 (86)	9/16 (56)

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Pediatric Patients

Infections Due to Gram-positive Organisms

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 1053
 1054 A safety and efficacy study provided experience on the use of ZYVOX in pediatric patients
 1055 for the treatment of nosocomial pneumonia, complicated skin and skin structure infections,
 1056 catheter-related bacteremia, bacteremia of unidentified source, and other infections due to
 1057 Gram-positive bacterial pathogens, including methicillin-resistant and -susceptible
 1058 *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Pediatric patients
 1059 ranging in age from birth through 11 years with infections caused by the documented or
 1060 suspected Gram-positive organisms were enrolled in a randomized, open-label, comparator-
 1061 controlled trial. One group of patients received ZYVOX I.V. Injection 10 mg/kg every 8
 1062 hours (q8h) followed by ZYVOX for Oral Suspension 10 mg/kg q8h. A second group
 1063 received vancomycin 10 to 15 mg/kg IV every 6 to 24 hours, depending on age and renal
 1064 clearance. Patients who had confirmed VRE infections were placed in a third arm of the
 1065 study and received ZYVOX 10 mg/kg q8h IV and/or orally. All patients were treated for a
 1066 total of 10 to 28 days and could receive concomitant Gram-negative antibiotics if clinically
 1067 indicated. In the intent-to-treat (ITT) population, there were 206 patients randomized to
 1068 linezolid and 102 patients randomized to vancomycin. One hundred seventeen (57%)
 1069 linezolid-treated patients and 55 (54%) vancomycin-treated patients were clinically
 1070 evaluable. The cure rates in ITT patients were 81% in patients randomized to linezolid and
 1071 83% in patients randomized to vancomycin (95% Confidence Interval of the treatment
 1072 difference; -13%, 8%). The cure rates in clinically evaluable patients were 91% in
 1073 linezolid-treated patients and 91% in vancomycin-treated patients (95% CI; -11%, 11%).
 1074 Modified intent-to-treat (MITT) patients included ITT patients who, at baseline, had a
 1075 Gram-positive pathogen isolated from the site of infection or from blood. The cure rates in
 1076 MITT patients were 80% in patients randomized to linezolid and 90% in patients
 1077 randomized to vancomycin (95% CI; -23%, 3%). The cure rates for ITT, MITT, and

1078 clinically evaluable patients are presented in Table 20. After the study was completed, 13
1079 additional patients ranging from 4 days through 16 years of age were enrolled in an open-
1080 label extension of the VRE arm of the study. Table 21 provides clinical cure rates by
1081 pathogen for microbiologically evaluable patients including microbiologically evaluable
1082 patients with vancomycin-resistant *Enterococcus faecium* from the extension of this study.
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Table 20. Cure Rates at the Test-of-Cure Visit for Intent to Treat, Modified Intent to Treat, and Clinically Evaluable Pediatric Patients by Baseline Diagnosis

Population	ITT		MITT*		Clinically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)
Any diagnosis	150/186 (81)	69/83 (83)	86/108 (80)	44/49 (90)	106/117 (91)	49/54 (91)
Bacteremia of unidentified source	22/29 (76)	11/16 (69)	8/12 (67)	7/8 (88)	14/17 (82)	7/9 (78)
Catheter-related bacteremia	30/41 (73)	8/12 (67)	25/35 (71)	7/10 (70)	21/25(84)	7/9 (78)
Complicated skin and skin structure infections	61/72 (85)	31/34 (91)	37/43 (86)	22/23 (96)	46/49 (94)	26/27 (96)
Nosocomial pneumonia	13/18 (72)	11/12 (92)	5/6 (83)	4/4 (100)	7/7 (100)	5/5 (100)
Other infections	24/26 (92)	8/9 (89)	11/12 (92)	4/4 (100)	18/19 (95)	4/4 (100)

* MITT = ITT patients with an isolated Gram-positive pathogen at baseline

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Table 21. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Pediatric Patients with Infections due to Gram-positive Pathogens

Pathogen	Microbiologically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)
Vancomycin-resistant <i>Enterococcus faecium</i>	6/8 (75)*	0/0 (-)
<i>Staphylococcus aureus</i>	36/38 (95)	23/24 (96)
Methicillin-resistant <i>S. aureus</i>	16/17 (94)	9/9 (100)
<i>Streptococcus pyogenes</i>	2/2 (100)	1/2 (50)

* Includes data from 7 patients enrolled in the open-label extension of this study.

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1128 LAB-0139-20.1

1129 Revised November 2011

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