

## Clinical Policy: Linezolid (Zyvox)

Reference Number: ERX.NPA.24

Effective Date: 06.01.15

Last Review Date: 05.21

Line of Business: Commercial, Medicaid

[Revision Log](#)

**See Important Reminder at the end of this policy for important regulatory and legal information.**

### Description

Linezolid (Zyvox<sup>®</sup>) is an oxazolidinone-class antibacterial agent.

### FDA Approved Indication(s)

Zyvox is indicated in adults and children for the treatment of the following infections caused by susceptible gram-positive bacteria:

- Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates) or *Streptococcus pneumoniae*
- Community-acquired pneumonia caused by *Streptococcus pneumoniae*, including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible isolates only)
- Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Zyvox has not been studied in the treatment of decubitus ulcers
- Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*
- Vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia

Limitations of Use:

- Zyvox is not indicated for the treatment of Gram-negative infections.
- The safety and efficacy of Zyvox formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

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

### Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions<sup>™</sup> that Zyvox is **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. All FDA-Approved Indications (must meet all):

1. Diagnosis is an FDA-approved indication;
2. Member meets one of the following (a or b):
  - a. Request is for continuation of therapy initiated in an acute care hospital from which member was discharged;
  - b. Both of the following (i and ii):
    - i. Culture and sensitivity (C&S) report for the current infection shows isolated pathogen is a gram-positive bacteria susceptible to linezolid, unless provider submits documentation that obtaining a C&S report is not feasible;

- ii. Member meets one of the following (a, b, or c):
  - a) Failure of  $\geq 2$  formulary antibiotics to which the isolated pathogen is susceptible (if available) per C&S report, unless all are contraindicated or clinically significant adverse effects are experienced;
  - b) C&S report shows resistance or lack of susceptibility of the isolated pathogen to all formulary antibiotics FDA-approved for member's diagnosis;
  - c) If provider documents that obtaining a C&S report is not feasible: Failure of  $\geq 2$  formulary antibiotics indicated for member's diagnosis (if available), unless all are contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed 1,200 mg (2 tablets, 2 vials, or 60 mL suspension) per day.

**Approval duration: Duration of request or up to 28 days of total treatment, whichever is less**

**B. Multi-Drug Resistant Tuberculosis (off-label) (must meet all):**

1. Diagnosis of pulmonary multi-drug resistant tuberculosis (MDR-TB) or extensively drug resistant tuberculosis (XDR-TB);
2. Prescribed by or in consultation with an infectious disease specialist, pulmonologist, or expert in the treatment of tuberculosis (e.g., state or county public health department, specialists affiliated with TB Centers of Excellence as designated by the CDC, infectious disease specialists managing TB clinics);
3. Dose does not exceed 1,200 mg (2 tablets) per day.

**Approval duration: 6 months**

**C. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. All FDA-Approved Indications (must meet all):**

1. Member meets one of the following (a or b):
  - a. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
  - b. Request is for continuation of therapy initiated in an acute care hospital from which member was discharged;
2. Member is responding positively to therapy;
3. Member has not received  $\geq 28$  days of therapy for current infection;
4. If request is for a dose increase, new dose does not exceed 1,200 mg (2 tablets, 2 vials, or 60 mL suspension) per day.

**Approval duration: Up to 28 days of total treatment**

**B. Multi-Drug Resistant Tuberculosis (off-label) (must meet all):**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 1,200 mg (2 tablets) per day.

**Approval duration: Up to a total treatment duration of 24 months**

**C. Other diagnoses/indications (must meet 1 or 2):**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.  
**Approval duration: Duration of request or 28 days (whichever is less); or**
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

C&S: culture and sensitivity

FDA: Food and Drug Administration

MDR-TB: multi-drug resistant tuberculosis

XDR-TB: extensively drug resistant tuberculosis

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria.*

*The drugs listed here may not be a formulary agent and may require prior authorization.*

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Therapeutic alternatives include formulary antibiotics that are indicated for member’s diagnosis and have sufficient activity against the offending pathogen at the site of the infection.		

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - Known hypersensitivity to linezolid or any of the other product components
  - Patients taking any monoamine oxidase inhibitors (MAOI) within two weeks of taking an MAOI
- Boxed warnings(s): none reported

*Appendix D: General Information*

For MDR-TB or XDR-TB:

- CDC Centers of Excellence for TB: [https://www.cdc.gov/tb/education/tb\\_coe/default.htm](https://www.cdc.gov/tb/education/tb_coe/default.htm)
- Pretomanid should only be used in combination with Sirturo and linezolid.
- Dosing of the combination regimen of pretomanid, Sirturo, and linezolid can be extended beyond 26 weeks if necessary, to a maximum of 9 months, in patients with delayed culture conversion.
  - Delayed culture conversion: two consecutive negative sputum cultures following an initial positive culture.
- Laboratory confirmation of multi-drug resistant TB must show TB with an isolate showing genotypic or phenotypic resistance to isoniazid and rifampin.
- Laboratory confirmation of extensively drug resistant TB must show TB with an isolate showing genotypic or phenotypic resistance to isoniazid, rifampin, fluoroquinolones, as well as second-line injectable agents such as aminoglycosides or capreomycin.
- Linezolid starting dose of 1,200 mg daily for 26 weeks may be managed as follows:
  - Adjusted to 600 mg daily and further reduced to 300 mg daily as necessary for adverse reactions of myelosuppression, peripheral neuropathy, and optic neuropathy.
  - Doses of the regiment missed for safety reasons can be made up at the end of treatment; does of linezolid alone missed due to adverse reactions should not be made up.

## V. Dosage and Administration

Indication	Dosing Regimen			Maximum Dose
	Pediatrics (birth – age 11 years)	Adults and Adolescents (age ≥ 12 years)	Duration (consecutive days)	
Nosocomial pneumonia Community-acquired pneumonia, including concurrent bacteremia Complicated skin and skin structure infections	10 mg/kg IV or PO every 8 hours	600 mg IV or PO every 12 hours	10 to 14	Adults and adolescents age ≥ 12 years: 1,200 mg/day
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg IV or PO every 8 hours	600 mg IV or PO every 12 hours	14 to 28	Age 1 – 11 years: 10 mg/kg/dose PO or IV every 8 hours (max: 600 mg/dose)
Uncomplicated skin and skin structure infections	Age < 5 years: 10 mg/kg PO every 8 hours Age 5 – 11 years: 10 mg/kg PO every 12 hours	Adults: 400 mg PO every 12 hours Adolescents: 600 mg PO every 12 hours	10 to 14	Infants and neonates: 10 mg/kg/dose PO or IV every 8 hours
MDR-TB or XDR-TB (off-label)	Administer in combination with Sirturo and pretomanid in a directly observed therapy (DOT) setting. <ul style="list-style-type: none"> <li>Sirturo: 400 mg PO QD for the first 2 weeks, followed by 200 mg PO three times per week (with at least 48 hours between doses) for 24 weeks (total duration of 26 weeks).</li> <li>Pretomanid: 200 mg PO QD for 26 weeks.</li> <li>Linezolid: 1,200 mg PO QD for 26 weeks.</li> </ul>			1,200 mg/day

## VI. Product Availability

- Injection: 200 mg/100 mL and 600mg /300 mL
- Tablet: 600 mg
- Oral suspension: 100 mg/5 mL

## VII. References

1. Zyvox Prescribing Information. New York, NY: Pfizer Inc.; October 2020. Available at: <http://labeling.pfizer.com/showlabeling.aspx?id=649> Accessed November 24, 2020.
2. Linezolid Drug Monograph. Clinical Pharmacology. Accessed November 2020. <http://www.clinicalpharmacology-ip.com/>.
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4. Ament PW, Jamshed, N., Horne JP. Linezolid: its role in the treatment of gram-positive, drug-resistant bacterial infections. Am Fam Physician. 2002 Feb 15;65(4):663-671. [www.aafp.org/afp/20020215/663.html](http://www.aafp.org/afp/20020215/663.html).
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6. Pretomanid Prescribing Information. Hyderabad, India: Mylan; August 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/212862s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf). Accessed September 6, 2019.

7. FDA Briefing Document for Pretomanid tablet, 200mg. Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC): New York, NY: June 6, 2019. Available at: <https://www.fda.gov/media/127592/download>. Accessed September 6, 2019.
8. Pretomanid: Sponsor Briefing Document Antimicrobial Drugs Advisory Committee. New York, NY: June 6, 2019. Available at: <https://www.fda.gov/media/127593/download>. Accessed September 6, 2019.
9. Metlay J, Waterer G, Long A, et al. Diagnosis and treatment of adults with community-acquired pneumonia: An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of American. American Thoracic Society Documents. Oct 2019; 200(7):e45-67

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template; added prescriber specialty; modified criteria to allow for cases in which obtaining C&S report is not feasible per documentation from the provider; consolidated requirements for VRE/MRSA and non-VRE/MRSA- modified criterion related to VRE or MRSA to require failure of 2 formulary antibiotics (instead of 1), provided 2 appropriate formulary antibiotics are available; added safety requirement related to contraindications per PI; updated generalized FDA max statement to specific max dose of drug.	06.17	08.17
2Q 2018 annual review: No clinically significant changes; Updated per safety guidance; References reviewed and updated.	03.06.18	05.18
1Q 2019 annual review: added criterion line for diagnosis to be an FDA-approved indication; removed 7 day requirement for C&S report and replaced it with requirement that C&S report is for the current infection; clarified that pathogen susceptibility to antibiotics be demonstrated via C&S report; added 'lack of susceptibility' as an alternative to demonstrating resistance on C&S; removed criterion allowing member to meet criteria if formulary antibiotics are not indicated for member's diagnosis, since this is incorporated into other existing criteria already; added criterion to allow member to continue treatment if it was started in an acute care hospital and member was discharged; references reviewed and updated.	10.30.18	02.19
1Q 2020 annual review: criteria added for treatment of multi-drug resistant and extensively drug resistant TB with pretomanid; added general information regarding all oral combination regimen of pretomanid, bedaquiline, and linezolid based on FDA briefing document; removed specialist requirement from FDA-approved indications; references reviewed and updated.	10.30.19	02.20
RT4: added limitations of use per PI update	08.25.20	
1Q 2021 annual review: no significant changes; updated product availability; updated dosage and administration; references reviewed and updated	11.24.20	02.21
For TB indication, per IDSA/WHO 2019 guidelines for MDR-TB removed requirements for age limit, use in combination with bedaquiline and pretomanid, and fluoroquinolone resistance; revised continued authorization to up to 24 months; added pulmonologist and expert in the treatment of tuberculosis as an additional specialist prescriber options.	04.06.21	05.21

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of

physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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