

**Clinical Policy: Linezolid (Zyvox)**

Reference Number: CP.PMN.27

Effective Date: 09.01.06

Last Review Date: 02.23

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)[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

Limitation(s) of use:

- Zyvox 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
- 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 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. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**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.*

It is the policy of health plans affiliated with Centene Corporation<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 clinically significant adverse effects are experienced or all are contraindicated;
      - 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 clinically significant adverse effects are experienced or all are contraindicated;
3. Dose does not exceed both of the following (a and b):
  - a. 1,200 mg per day;
  - b. 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. Pulmonary Multi-Drug Resistant Tuberculosis and Extensively 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 both of the following (a and b):
  - a. 1,200 mg per day;
  - b. 2 tablets per day.

**Approval duration: 6 months**

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
  - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
  - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

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

1. Member meets one of the following (a, b, or c):
  - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
  - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
  - c. 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 exceed both of the following (a and b):
  - a. 1,200 mg per day;
  - b. 2 tablets, 2 vials, or 60 mL suspension per day.

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

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

1. Member meets one of the following (a or b):
  - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
  - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
2. Member is responding positively to therapy;

3. If request is for a dose increase, new dose does not exceed both of the following (a and b):
  - a. 1,200 mg per day;
  - b. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
  - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
  - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

C&S: culture and sensitivity	MDR-TB: multi-drug resistant tuberculosis
CDC: Centers for Disease Control and Prevention	XDR-TB: extensively drug resistant tuberculosis
FDA: Food and Drug Administration	

*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 for all relevant lines of business 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<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) 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 with pretomanid:

- Centers for Disease Control and Prevention (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; doses 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  Age 1 – 11 years: 10 mg/kg/dose PO or IV every 8 hours (max: 600 mg/dose)
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	
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 with pretomanid (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
- Tablets: 600 mg
- Oral suspension: 100 mg/5 mL

**VII. References**

1. Zyvox Prescribing Information. New York, NY; Pfizer Inc.; October 2021. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/021130s042,021131s038,021132s041lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021130s042,021131s038,021132s041lbl.pdf). Accessed October 5, 2022.
2. Linezolid Drug Monograph. Clinical Pharmacology. Available at: [www.clinicalkeys.com/pharmacology](http://www.clinicalkeys.com/pharmacology). Accessed October 5, 2022.
3. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis 2014; Jul 15;59(2):147-59.
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5. C Liu, et al. Management of patients with infections caused by methicillin-resistant Staphylococcus aureus: clinical practice guidelines by the Infectious Diseases Society of America (IDSA). Clinical Infectious Diseases; 2011;52:1-38.
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 October 5, 2022.
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 October 5, 2022.
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 October 5, 2022.
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.
10. WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. 15 June 2020. Available at: <https://www.who.int/publications/i/item/9789240007048>. Accessed October 5, 2022.

**Coding Implications**

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2020	Injection, linezolid, 200 mg
J2021	Injection, linezolid (hospira) not therapeutically equivalent to J2020, 200 mg



Reviews, Revisions, and Approvals	Date	P&T Approval Date
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 that linezolid should be prescribed by or in consultation with an ID specialist; references reviewed and updated; revised HIM line of business.	09.19.19	02.20
RT4: added limitations of use per PI update	08.25.20	
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; 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
1Q 2022 annual review: added Commercial line of business to policy; references reviewed and updated.	09.23.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.20.22	
1Q 2023 annual review: no significant changes; references reviewed and updated. Updated HCPCS code [J2021].	10.05.22	02.23

**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. The Health Plan makes no representations and



accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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**Note:**

**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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