Clinical Policy: Linezolid (Zyvox)

Reference Number: CP.PMN.27
Effective Date: 09.01.06
Last Review Date: 08.25
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®) 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® that linezolid and Zyvox are **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):*
      **For Illinois HIM requests, the step therapy requirements below do not apply for formulary agents as of 1/1/2026 per IL HB 5395.*
         a) Failure of ≥ 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 ≥ 2 formulary antibiotics indicated for member's diagnosis (if available), unless clinically significant adverse effects are experienced or all are contraindicated;
3. If request is for orally administered brand Zyvox, member must use generic linezolid, unless contraindicated or clinically significant adverse effects are experienced;
4. 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. If request is for orally administered brand Zyvox, member must use generic linezolid, unless contraindicated or clinically significant adverse effects are experienced;
4. 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 ≥ 28 days of therapy for current infection;
4. If request is for orally administered brand Zyvox, member must use generic linezolid, unless contraindicated or clinically significant adverse effects are experienced;
5. 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 orally administered brand Zyvox, member must use generic linezolid, unless contraindicated or clinically significant adverse effects are experienced;
4. 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
CDC: Centers for Disease Control and Prevention
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 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® (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 with pretomanid:

- Centers for Disease Control and Prevention (CDC) Centers of Excellence for TB: https://www.cdc.gov/tb-programs/php/about/tb-coe.html?CDC_AAref_Val=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, based on delayed treatment response within the first 8 weeks as assessed by time to culture conversion (delayed culture conversion), persistent culture positivity, clinical response to treatment, and other underlying clinical factors, or modified based on adverse events.
  - 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.

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			10 to 14	

Indication	Dosing Regimen			Maximum Dose
	Pediatrics (birth – age 11 years)	Adults and Adolescents (age ≥ 12 years)	Duration (consecutive days)	
Community-acquired pneumonia, including concurrent bacteremia	10 mg/kg IV or PO every 8 hours	600 mg IV or PO every 12 hours		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) Infants and neonates: 10 mg/kg/dose PO or IV every 8 hours
Complicated skin and skin structure infections				
Vancomycin-resistant *Enterococcus faecium* 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	
MDR-TB or XDR-TB with pretomanid (off-label)	Administer in combination with Sirturo and pretomanid in a directly observed therapy (DOT) setting. • 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). • Pretomanid: 200 mg PO QD for 26 weeks. • Linezolid: 600 mg PO QD for 26 weeks.			1,200 mg/day

VI. Product Availability

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

VII. References

1. Zyvox Prescribing Information. New York, NY; Pfizer Inc.; June 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021130s046,021131s044,021132s046lbl.pdf. Accessed April 21, 2025.

2. Pretomanid Prescribing Information. Hyderabad, India: Mylan; December 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212862s004lbl.pdf. Accessed April 21, 2025.
3. Linezolid Drug Monograph. Clinical Pharmacology. Available at: www.clinicalkeys.com/pharmacology. Accessed May 15, 2024.
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6. 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.
7. FDA Briefing Document for Pretomanid tablet, 200mg. Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC): New York, NY: June 6, 2019.
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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 May 11, 2023.
11. Provisional CDC Guidance for the Use of Pretomanid as part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease. May 4, 2023 (Updated February 8, 2024). Available at: https://www.cdc.gov/tb/topic/drtb/bpal/default.htm. Accessed May 15, 2024.
12. Senneville E, Albalawi Z, van Asten SA, et al. IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections. October 2, 2023. Available at: https://www.idsociety.org/practice-guideline/diabetic-foot-infections/. Accessed May 16, 2024.
13. WHO-Key updates to the treatment of drug-resistant tuberculosis: rapid communication, June 2024. Available at: https://www.who.int/publications/i/item/B09123. Accessed May 13, 2025.
14. Center for Disease Control and Prevention. Treating Drug-resistant Tuberculosis Disease. Updated May 6, 2024. Available at: https://www.cdc.gov/tb/treatment/drug-resistant-tuberculosis.html?CDC_AAref_Val=https://www.cdc.gov/tb/topic/drtb/default.htm. Accessed May 13, 2025.

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 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
3Q 2023 annual review: no significant changes; in Section V MDR-TB or XDR-TB dosing, modified linezolid initial dose from 1,200 mg to 600 mg per CDC recommendations; references reviewed and updated.	04.12.23	08.23
3Q 2024 annual review: added requirement if request is for orally administered brand Zyvox, member must use generic linezolid; references reviewed and updated.	05.06.24	08.24
3Q 2025 annual review: no significant changes; added references to generic linezolid in Policy/Criteria description as criteria would apply; added step therapy bypass for IL HIM per IL HB 5395; references reviewed and updated.	04.21.25	08.25

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.