Clinical Policy: Linezolid (Zyvox)

Reference Number: CP.PMN.27
Effective Date: 09.01.06
Last Review Date: 05.21
Line of Business: 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.
- 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.

It is the policy of health plans affiliated with Centene Corporation® 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 ≥ 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 ≥ 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. **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 1,200 mg (2 tablets) per day.

      Approval duration: 6 months

   C. **Other diagnoses/indications**
      1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): 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 or b):

a. Currently receiving medication via Centene benefit 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 ≥ 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. Pulmonary Multi-Drug Resistant Tuberculosis and Extensively Drug Resistant Tuberculosis (off-label) (must meet all)**:**

1. Currently receiving medication via Centene benefit 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) daily.

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 Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 28 days (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): 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 – 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
pretomanid	200 mg PO QD for 26 weeks.	200 mg/day
Sirturo® (bedaquiline)	400 mg PO QD for the first 2 weeks, followed by 200 mg PO three times per week for remaining 24 weeks.	400 mg/day
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/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 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
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: 1,200 mg PO QD for 26 weeks.			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 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.
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.
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.
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. 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

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Clinical changes made to criteria: Modified criteria to allow for cases in which obtaining C&S report is not feasible per documentation from the provider Removed language specifying "Isolated pathogen is VRE" since VRE is gram-positive and policy covers gram positive bacteria Added max dose requirement in initial approval criteria	01.17	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Non-clinical changes made: Converted to new template Updated policy name to reflect linezolid tablets since the oral suspension is on the formulary and does not require a PA Updated references		
2Q 2018 annual review: no significant changes; safety updated per safety guidance endorsed by Centene Medical Affairs; 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 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

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.