Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 02/01/2022**
Policy Number: PA.CP.PMN.27	**Effective Date: 01/2018** **Revision Date: 01/2022**
Policy Name: Linezolid (Zyvox)	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ☐ **Revised Policy***
- ✓ **Annual Review - No Revisions**
- ☐ **Statewide PDL -** *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

1Q 2022 annual review: references reviewed and updated.

Name of Authorized Individual (Please type or print): **Venkateswara R. Davuluri, MD**	**Signature of Authorized Individual:**

Clinical Policy: Linezolid (Zyvox)

Reference Number: PA.CP.PMN.27
Effective Date: 01/2018
Last Review Date: 01/2022

Coding Implications
Revision Log

Description
Linezolid (Zyvox®) is an oxazolidinone-class antibacterial agent.

FDA approved indication
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 (including office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of Pennsylvania Health and Wellness® that Zyvox tablets and/or oral suspension are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria (must meet all):
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 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. 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 – Refer to PA.CP.PMN.53 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 Pennsylvania Health and Wellness benefit; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
   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 Pennsylvania Health and Wellness benefit; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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 Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
   Approval duration: Duration of request or up to 28 days of total treatment (whichever is less); or
2. Refer to PA.CP.PMN.53 if requested indication is NOT 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 – PA.CP.PMN.53 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.; September 2021. Available at: http://labeling.pfizer.com/showlabeling.aspx?id=649 Accessed September 23, 2021.
2. Linezolid Drug Monograph. Clinical Pharmacology. http://www.clinicalpharmacology-ip.com. Accessed September 23, 2021.
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 23, 2021.
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 23, 2021.
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 September 23, 2021.

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	Approval Date
2Q 2018 annual review: modified criteria to allow for cases in which obtaining C&S report is not feasible per documentation from the	03.06.18	

Reviews, Revisions, and Approvals	Date	Approval Date
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; references reviewed and updated.		
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.	01.19	
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.	01/2020	
1Q 2021 annual review: added limitations of use per PI update; references reviewed and updated	01/2021	
For TB indication, added pulmonologist and expert in the treatment of tuberculosis as an additional specialist prescriber options.	07/2021	
1Q 2022 annual review: references reviewed and updated.	01/2022	