Drug Coverage Policy

Effective Date.....4/1/2025
Coverage Policy Number.....IP0372
Policy Title.....Linezolid (Zyvox), Sivextro

Antibiotics – Linezolid (Zyvox), Sivextro

- linezolid (tablets and oral suspension)
- Zyvox® (linezolid tablets and oral suspension - Pfizer, generic)
- Sivextro™ (tedizolid phosphate tablets – Cubist Pharmaceuticals)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

Overview
Linezolid (Zyvox) and Sivextro are synthetic oxazolidinone antimicrobial agents.[1,2] Both agents have clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. Cross-resistance between linezolid or Sivextro and other classes of antibiotics is unlikely because the mechanism of action for both of these agents differs from that of other antibacterial agents.

Linezolid is indicated in adults and children for the treatment of the following infections caused by susceptible strains of the designated microorganisms:[1.]

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

Limitation of Use: Linezolid is not indicated for the treatment of Gram-negative infections. It is crucial that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. The safety and efficacy of linzezolid given longer than 28 days have not been evaluated in controlled clinical trials.

Sivextro is indicated for the treatment of **acute bacterial skin and skin structure infections** (ABSSSI) that are caused by susceptible isolates of the following Gram-positive microorganisms: *S. aureus* (MRSA and MSSA), *S. pyogenes*, *S. agalactiae*, *Streptococcus anginosus* Group (including *S. anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis* in adults and pediatric patients ≥ 12 years of age.[2]

Although linezolid and Sivextro are indicated for the treatment of infections caused by susceptible strains of MSSA and drug-resistant strains of *S. pneumoniae* in some situations, these agents are not the optimal drug or drugs of first choice for these microorganisms.[3,4] Other antibiotics may be used. In efforts to reduce the development of drug-resistant bacteria and maintain effectiveness of linezolid and Sivextro, both antibiotics should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.[1,2] 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.

Guidelines

Linezolid and Sivextro are addressed in a number of guidelines from the Infectious Diseases Society of America (IDSA):

- ***Diabetic Foot Infections:*** A clinical practice guideline for the diagnosis and treatment of diabetic foot infections (2023) notes that diabetic foot infections of moderate severity may be treated with oral or initial parenteral therapy, whereas severe infections should be treated with parenteral therapy.[6] Linezolid, Cubicin® (daptomycin injection), doxycycline, clindamycin, fluoroquinolones and intravenous (IV) vancomycin are listed as therapy options for infections caused by MRSA.
- ***Infective Endocarditis:*** Treatment guidelines, from the American Heart Association and endorsed by IDSA (2015), recommend linezolid as a treatment option for patients with infective endocarditis caused by *Enterococcus* species that is resistant to penicillin, aminoglycosides, and vancomycin.[9]
- ***MRSA:*** Guidelines (2011) for the treatment of MRSA infections recognize linezolid as a treatment option for infections, including those involving the central nervous system (e.g., meningitis, brain abscess), osteomyelitis, and septic arthritis.[5]
- ***Multidrug-Resistant Tuberculosis:*** Treatment guidelines from the World Health Organization (2022) recommend linezolid to be used in combination with Pretomanid and

Sirturo (bedaquiline tablets) for 6 to 9 months for the treatment of multidrug-resistant tuberculosis or rifampin-resistant tuberculosis.[10]

- ***Pneumonia:*** Guidelines from the American Thoracic Society (ATS) and IDSA (2016) recommend that MRSA hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) be treated with either vancomycin or linezolid rather than other antibiotics or other antibiotic combinations.[4] The choice between vancomycin and linezolid may be guided by patient-specific factors such as blood cell counts, concurrent prescriptions for serotonin reuptake inhibitors, renal function, and cost. The available evidence indicates that vancomycin and linezolid are roughly similar, and no alternative agent or regimen is clearly superior to these two products. Guidelines from IDSA/ATS (2019) for CAP recommend vancomycin or linezolid for the treatment of community-acquired MRSA.[3] In addition, the Pediatric Infectious Diseases Society and IDSA guidelines (2011) for the treatment of CAP in infants and children > 3 months of age recommend linezolid as an alternative to vancomycin for treatment of MRSA, and as an alternative to ceftriaxone for the treatment of *S. pneumoniae* resistant to penicillin.[8]
- ***SSTIs:*** Guidelines (2014) for the diagnosis and management of SSTIs recommend oral antibiotics such as penicillin VK, cephalosporin, dicloxacillin, and clindamycin for mild nonpurulent (i.e., necrotizing infection, cellulitis, erysipelas) SSTIs.[7] For moderate nonpurulent SSTI, IV antibiotics such as penicillin, ceftriaxone, cefazolin, and clindamycin are recommended. For moderate purulent SSTIs, empiric treatment can be started with trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline. For MRSA infections, TMP/SMX is the recommended therapy. Cephalexin or dicloxacillin are usually effective for MSSA infections. For severe purulent SSTI, empiric therapy with IV vancomycin, Cubicin, linezolid, Vibativ® (telavancin intravenous infusion), or Teflaro® (ceftaroline intravenous infusion) are recommended. All of these agents are active against MRSA strains. For severe purulent SSTIs caused by MSSA, therapy can be switched to nafcillin, cefazolin, or clindamycin.

Medical Necessity Criteria

I. Linezolid (Zyvox) is considered medically necessary when ONE of the following are met (1, 2, 3, 4, or 5):

FDA-Approved Indications

1. **Methicillin-Resistant *Staphylococcus* Species Infection, Treatment**. Approve for 1 month in patients who meet the following:
   - **A.** Preferred product criteria are met for the product(s) as listed in the below table(s).

2. **Vancomycin-Resistant *Enterococcus* Species Infection, Treatment**. Approve for 1 month in patients who meet the following:
   - **A.** Preferred product criteria are met for the product(s) as listed in the below table(s).

Other Uses with Supportive Evidence

3. **Continuation of Linezolid Therapy.** Approve for 1 month in patients who meet BOTH of the following (A and B):
   - **A.** ONE of the following (i or ii):

i. Patient is transitioning from intravenous (IV) linezolid or IV vancomycin to oral linezolid therapy; OR

ii. Patient was started on oral linezolid in an inpatient facility and is continuing therapy.

B. Preferred product criteria are met for the product(s) as listed in the below table(s).

4. **Treatment of an Infection that is Resistant to Other Antibiotics, but the Organism is Sensitive to Linezolid.** Approve for 1 month in patients who meet the following:
   A. Preferred product criteria are met for the product(s) as listed in the below table(s).

5. **There is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber or Representative Cannot be Contacted.** Approve for up to 2 weeks of therapy.

   To avoid delays or disruption in therapy for the patient, if there is insufficient information available to make a determination regarding coverage and the prescriber or representative of the prescriber cannot be contacted, approve linezolid for up to 2 weeks.

6. **Tuberculosis.** Approve for 9 months if the patient meets **ALL** of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i, ii, or iii):
      i. Patient has extensively drug-resistant tuberculosis; OR
      ii. Patient has treatment-intolerant tuberculosis; OR
      iii. Patient has nonresponsive multidrug-resistant tuberculosis; AND
   C) Linezolid is prescribed in combination with Sirturo (bedaquiline tablets) and Pretomanid tablets.
   D) Preferred product criteria are met for the product(s) as listed in the below table(s).

Individual and Family Plans:

Product	Criteria
Zyvox (linezolid) tablets	Trial of **linezolid tablet** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction.
Zyvox (linezolid) oral suspension	Trial of **linezolid oral suspension** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction.

II. Sivextro is considered medically necessary when ONE of the following are met (1, 2, or 3):

FDA-Approved Indication

1. **Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA), Selected *Streptococcus* Species (i.e., *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus anginosus* Group) and *Enterococcus faecalis*.** Approve for up to 6 days in patients who meet the following:
    A. Preferred product criteria is met for the product(s) as listed in the below table(s).

Other Uses with Supportive Evidence

2. **Continuation of Sivextro Therapy in the Outpatient Setting.** Approve for up to 6 days of therapy in patients transitioning from Sivextro IV therapy to oral therapy.

3. **There is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber or Representative Cannot be Contacted.** Approve for up to 6 days of therapy.

    To avoid delays or disruption in therapy for the patient, if there is insufficient information available to make a determination regarding coverage and the prescriber or representative of the prescriber cannot be contacted, approve Sivextro. Since the available data for Sivextro only supports up to 6 days of therapy for the ABSSSI indication, we are limiting approval to this duration.

Individual and Family Plans:

Product	Criteria
Sivextro (tedizolid) tablets	**ONE** of the following (1, 2, 3, or 4): 1. The patient has tried linezolid tablets or oral suspension. 2. The patient is currently taking a medication that interacts with linezolid (for example, monoamine oxidase inhibitors [MAOIs] or selective serotonin reuptake inhibitors [SSRIs]). 3. The patient is being treated for an organism that is resistant to linezolid, but sensitive to Sivextro. 4. The patient has been started on a course of therapy with Sivextro (to allow for completion of a course of therapy).

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

References

1. Zyvox® injection, tablets, and oral suspension [prescribing information]. New York, NY: Pfizer; June 2024.
2. Sivextro™ tablets [prescribing information]. Rahway, NJ: Merck; March 2023.
3. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200: e45-e67.
4. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-aquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016;63: e61–e111.
5. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis.* 2011; 52:1-38.
6. Senneville E, Albalawi Z, van Asten S, et al. IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDSA 2023). *CID.* 2023; ciad527.
7. 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;59: e10-e52.
8. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;53(7): e25-76.
9. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the committee on rheumatic fever, endocarditis, and rheumatic fever, Council on cardiovascular disease in the young, and the Councils on clinical cardiology, stroke, and cardiovascular surgery, and anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. *Circulation*. 2015; 132:1435-1486.
10. WHO consolidated guidelines on tuberculosis: Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Linezolid and Zyvox** Updated the authorization duration from 28 days to 1 month for Methicillin-Resistant Staphylococcus Species Infection, Treatment, Vancomycin-Resistant Enterococcus Species Infection, Treatment, Continuation of Linezolid Therapy and Treatment of an Infection that is Resistant to Other Antibiotics, but the Organism is Sensitive to Linezolid. **Added coverage for** patients where there is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber or Representative Cannot be Contacted. **Removed coverage for** Known or Suspected Multi-Drug Resistant Streptococcal Species Infection, Known or Suspected Multi-Drug Resistant Tuberculosis (MDR-TB) Infection, as Part of a Multi-Drug Regimen and Known or Suspected Nontuberculous Mycobacterial (or Atypical	07/01/2024

	Mycobacterial) Infection - when prescribed by, or in consultation with, an infectious disease specialist. **<u>Sivextro</u>** **Acute Bacterial Skin and Skin Structure Infections (ABSSSI)** Removed the prerequisite step through an appropriate first-line therapy. **Added coverage for** patients where there is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber or Representative Cannot be Contacted. **Added** a preferred product step through linezolid for IFP.	
Annual Revision	**Linezolid – Other Uses with Supportive Evidence:** **Tuberculosis:** This condition and criteria for approval was added to the policy under "Other Uses with Supportive Evidence."	4/1/2025

The policy effective date is in force until updated or retired.