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. 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.

Coverage Policy
This coverage policy addresses the use of oral linezolid and tedizolid. The use of intravenous linezolid and tedizolid are not addressed in this coverage policy.

Linezolid (Zyvox®) is considered medically necessary for the treatment of a known or suspected gram-positive infection caused by ANY of the following:
- Methicillin-resistant Staphylococcus infections (for example, MRSA/ORSA, MRSE/ORSE)
- Vancomycin-resistant Enterococcus (VRE)
- Multi-drug resistant Streptococcal infections
- Multi-drug resistant tuberculosis (MDR-TB) infection, as part of a multi-drug regimen
- Nontuberculous atypical mycobacterial infections when prescribed by, or in consultation with, infectious disease specialist

For Individual and Family Plans the following criteria must be met in addition to the criteria above:
- Zyvox (linezolid) tablets are covered when there is documented intolerance to 1 generic formulation of Zyvox tablets.
- Zyvox (linezolid) suspension is covered when there is documented intolerance to 1 generic formulation of Zyvox suspension.
Tedizolid phosphate (Sivextro®) is considered medically necessary when the following criteria are met:

- Treatment of acute bacterial skin and skin structure infections (ABSSSI) for EITHER of the following:
  - Continuation therapy of documented Sivextro initiated by IV infusion
  - Documented failure, contraindication per FDA label, or intolerance to appropriate first-line therapy (for example: ceftriaxone, cefazolin, cephalaxin, clindamycin, linezolid, piperacillin-tazobactam, vancomycin)

Authorization is for a single course of therapy as follows:

- Linezolid for a treatment duration up to 28 days
- Tedizolid phosphate for a treatment duration up to 6 days

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.

Linezolid and tedizolid phosphate are considered experimental, investigational, or unproven for any other use including the following:

- Treatment of gram-negative infections

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

FDA Approved Indications

FDA Approved Indication

**Zyvox**

Zyvox is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. 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.

- **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.

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 infections that are proven or strongly suspected to be caused by susceptible 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.

The safety and efficacy of Zyvox formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

**Sivextro**

Sivextro is an oxazolidinone-class antibacterial indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: Staphylococcus aureus (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates),
Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus Group (including Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus), and Enterococcus faecalis.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Sivextro and other antibacterial drugs, Sivextro should be used only to treat ABSSSI that are proven or strongly suspected to be caused by susceptible 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.

**Recommended Dosing**

**FDA Recommended Dosing**

**Zyvox**

<table>
<thead>
<tr>
<th>Infection*</th>
<th>Dosage Guidelines for Zyvox</th>
<th>Recommended Duration of Treatment (consecutive days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage, Route and Frequency of Administration</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Pediatric Patients† (Birth through 11 Years of Age)</strong></td>
<td></td>
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</tr>
<tr>
<td>Nosocomial pneumonia</td>
<td>10 mg/kg intravenously or oral‡ every 8 hours</td>
<td>10 to 14</td>
</tr>
<tr>
<td>Community-acquired pneumonia, including concurrent bacteremia</td>
<td>600 mg intravenously or oral‡ every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Complicate skin and skin structure infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin-resistant Enterococcus faecium infections, including concurrent bacteremia</td>
<td>10 mg/kg intravenously or oral‡ every 8 hours</td>
<td>14 to 28</td>
</tr>
<tr>
<td>Uncomplicated skin and skin structure infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 5 yrs: 10 mg/kg oral‡ every 8 hours</td>
<td>Adults: 400 mg oral‡ every 12 hours</td>
<td>10 to 14</td>
</tr>
<tr>
<td>5-11 yrs: 10 mg/kg oral‡ every 12 hours</td>
<td>Adolescents: 600 mg oral‡ every 12 hours</td>
<td></td>
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</tbody>
</table>

* Due to the designated pathogens
† Neonates less than 7 days: Most pre-term neonates less than 7 days of age (gestational age less than 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg every 12 hours. Consideration may be given to the use of 10 mg/kg every 8 hours regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg every 8 hours by 7 days of life.
‡ Oral dosing using either Zyvox Tablets or Zyvox for Oral Suspension.

No dose adjustment is necessary when switching from intravenous to oral administration.

**Sivextro**
The recommended dosage of Sivextro is 200 mg administered once daily for six (6) days either orally (with or without food) or as an intravenous (IV) infusion in patients 18 years of age or older.

No dose adjustment is necessary when changing from intravenous to oral Sivextro.

**Drug Availability**

**Zyvox**
Supplied as a 600 mg tablet of linezolid or as a powder for oral suspension that when reconstituted as directed, contains a total of 150 mL of a suspension at a concentration of 100 mg of linezolid per each 5 mL.

**Sivextro**
Supplied as a 200 mg tablet of tedizolid phosphate.
General Background

Pharmacology

**Zyvox**
Linezolid is an oxazolidinone antibiotic that has coverage primarily against aerobic gram-positive organisms, including vancomycin, methicillin, and penicillin-resistant microorganisms. It inhibits protein synthesis by binding to ribosomal RNA in the 50S subunit and prevents bacterial translation. Linezolid is rapidly and extensively absorbed after oral dosing with nearly 100% bioavailability and is readily distributed into well-perfused tissues. Linezolid is oxidized into two major inactive metabolites. (McEvoy, 2017)

**Sivextro**
Tedizolid is an oxazolidinone antibiotic that inhibits early steps of bacterial protein synthesis, binding the 50S ribosome, resulting in inhibition of bacterial translation and inhibition of protein synthesis. The phosphate prodrug is highly water soluble, which facilitates oral absorption and enhances bioavailability of tedizolid. Tedizolid has in vitro and clinical activity against S aureus (MSSA and MRSA), S anginosus group, β-hemolytic streptococci including S pyogenes and S agalactiae, and E faecalis. Cross-resistance may be possible between tedizolid and linezolid. (McEvoy, 2017)

Professional Societies/Organizations

The Infectious Diseases Society of America (IDSA) provides guidelines as described in the table below:

<table>
<thead>
<tr>
<th>IDSA Guideline</th>
<th>Recommendation</th>
<th>Year</th>
</tr>
</thead>
</table>
| Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children (Liu 2011) | Zyvox is recommended as follows:  
  - Empirical oral therapy for community-associated (CA) MRSA in outpatients with skin and soft-tissue infections (SSTIs).  
  - Oral treatment for both beta-hemolytic streptococci and CA-MRSA.  
  - IV treatment for hospitalized adult and pediatric patients with complicated SSTIs (cSSTIs; defined as patients with deeper soft-tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns), in addition to surgical debridement and broad-spectrum antibiotics.  
  - Zyvox should not be used in children if there is concern for infective endocarditis or endovascular source of  
    - IV or oral treatment for health care–associated (HA) MRSA or community-acquired MRSA pneumonia  
    - IV or oral treatment for osteomyelitis following surgical debridement and drainage of associated soft-tissue abscesses  
    - IV or oral treatment alternative (vancomycin recommended first-line) for meningitis, brain abscess, subdural empyema, or spinal epidural abscess, septic thrombosis of cavernous or dural venous sinus  
    - IV or oral to manage persistent MRSA bacteremia (if reduced susceptibility to vancomycin and daptomycin are demonstrated) and vancomycin treatment failures in adults | 2011  |
Clinical practice guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections (SSSI) (Stevens, 2014)

Empiric therapy for mild, nonpurulent SSSI includes an oral agent, typically either clindamycin, a macrolide (for example, erythromycin), a first or second generation cephalosporin (for example, cephalexin), or a semi-synthetic penicillin (for example, amoxicillin). Moderate and severe nonpurulent infections typically require intravenous (IV) antibiotics of the same classes with the addition of vancomycin. Any SSSI with a suspected causative organism of S aureus or any purulent SSSI should be assumed MRSA until susceptibility tests prove otherwise and treatment includes an agent active against MRSA (for example, vancomycin). *Tedizolid is introduced in the SSSI guideline as an investigational agent, place in therapy is not specified.

Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer (Freifeld, 2011)

Zyvox is recommended as an early addition to initial empirical therapy (treatment prior to determination of a firm diagnosis) for febrile patients with neutropenia with antibiotic resistant organisms including MRSA and VRE, particularly if the patient's condition is unstable or if the patient has positive blood culture results suspicious for resistant bacteria.

The World Health Organization (WHO) provides guidelines as described in the table below:

<table>
<thead>
<tr>
<th>WHO Guideline</th>
<th>Recommendation</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO treatment guidelines for drug-resistant tuberculosis - October 2016 Revision (Amanullah, 2016)</td>
<td>Linezolid is recommended for the treatment of multidrug-resistant tuberculosis, as a core second-line agent.</td>
<td>2018</td>
</tr>
</tbody>
</table>

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for gram-positive infection, drug resistant tuberculosis, nontuberculous atypical mycobacterial infection, or skin and skin structure infections.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for gram-positive infection, drug resistant tuberculosis, nontuberculous atypical mycobacterial infection, or skin and skin structure infections.

Off Label Uses

AHFS Drug Information 2019 Edition supports the following off-label use for linezolid: CNS infections caused by MRSA. However, AHFS does not support any off-label uses for tedizolid.

Experimental, Investigational, Unproven Uses

There is no evidence in the peer-reviewed published scientific literature to support safety and efficacy of linezolid or tedizolid for the treatment of gram-negative infections.

Coding/Billing Information

Note: Zyvox and Sivextro are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.
References