PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/20/2014
LAST REVIEW DATE: 11/18/2021
LAST CRITERIA REVISION DATE: 11/18/2021
ARCHIVE DATE:

Linezolid oral suspension and tablet
SIVEXTRO™ (tedizolid phosphate) oral tablet
ZYVOX® (linezolid) oral suspension and tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602)

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864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Criteria:

- **Criteria:** Sivextro (tedizolid) or Zyvox (linezolid) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with Infectious Disease, Dermatologist, Podiatrist, or Pulmonologist

2. Diagnosis is **ONE** of the following:
    a. **When applicable, to facilitate a hospital discharge**, individual is transitioning from intravenous therapy to oral therapy (the number of days of intravenous use is documented on the request)

    b. **For Sivextro (tedizolid)**: proven or strongly suspected acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible gram-positive bacteria per manufacturer label for individuals 12 years of age or older

    c. **For Zyvox (linezolid)**: proven or strongly suspected clinical infection caused by susceptible gram-positive bacteria per manufacturer label for **ANY** of the following infections:
        i. Nosocomial pneumonia (from *Streptococcus pneumonia* or *Staphylococcus aureus*)
        ii. Community-acquired pneumonia, including concurrent bacteremia (from *Streptococcus pneumonia* or *Staphylococcus aureus- methicillin sensitive* only)
        iii. Complicated skin and skin structure infections (**not** decubitus ulcers), including diabetic foot infection without concomitant osteomyelitis (from *Staphylococcus aureus* or *Streptococcus pyogenes* or *Streptococcus agalactiae*)
        iv. Uncomplicated skin and skin structure infections (from *Staphylococcus aureus- methicillin sensitive* only or *Streptococcus pyogenes*)
        v. Vancomycin-resistant *Enterococcus faecium* infection including concurrent bacteremia

3. Individual has failure, contraindication per FDA label, or intolerance to generic linezolid

4. Will not be used with or within two weeks of a mono-amine oxidase inhibitor (MAOI)

5. Will not be used in a patient taking serotonergic agents including serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, bupropion, or buspirone

Approval duration:

For Sivextro (tedizolid):

- Maximum duration regardless of route of administration: 6 days total (IV plus oral route)
- IV infusion: MEDICAL BENEFIT ONLY

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- No refills will be authorized
- Any request for refill will be reviewed as a new request

For Zyvox (linezolid):

- Maximum duration regardless of route of administration:
  - Most infections: 14 days total (IV plus oral route)
  - Vancomycin resistant *Enterococcus faecium* infection: 28 days total (IV plus oral route)
- IV infusion: MEDICAL BENEFIT ONLY
- No refills will be authorized
- Any request for refill will be reviewed as a new request

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of a Non-cancer Medications**

2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

This Pharmacy Coverage Guideline applies to the out-patient use of Sivextro and Zyvox, and should not be utilized for any other purpose.

Zyvox (linezolid) and Sivextro (tedizolid) are oxazolidinone-class antimicrobials used for the treatment of infections caused by susceptible isolates of gram-positive microorganisms. They 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, this information should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Prescribing either agent in the absence of a proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit to the individual and increases the risk of the development of drug-resistant bacteria.

Zyvox (linezolid) is indicated in adults and children for the treatment of the following infections caused by susceptible Gram-positive bacteria: Nosocomial pneumonia; Community-acquired pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; Uncomplicated skin and skin structure infections; and Vancomycin-resistant *Enterococcus faecium* infections.

Sivextro (tedizolid) is indicated in adult and pediatric patients 12 years of age and older 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*.
Acute bacterial skin and skin structure infections (ABSSSI) may include cellulitis, erysipelas, wound infections, burns, and major cutaneous abscesses. ABSSSI may present with redness, edema, or induration with lymph node enlargement, purulent drainage or pus within the dermis, and systemic symptoms such as fever.

Common bacterial pathogens causing ABSSSI are *Streptococcus pyogenes* and *Staphylococcus aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA). Less common causes include other *Streptococcus species*, *Enterococcus faecalis*, *Enterococcus faecium*, and Gram-negative bacteria. The incidence of gram positive ABSSSI that requires hospitalization has increased along with an increase in antimicrobial resistant organisms. MRSA has become a common cause of ABSSSI infections and pneumonia in the hospital setting. Infections in individuals who lack the usual risk factors for MRSA have also emerged in the community. As a result, community associated MRSA (CA-MRSA) are now a common cause of ABSSSI. Over reliance with use of Vancomycin has in addition resulted in emergence of resistant strains of certain bacteria such as Vancomycin resistant *Staphylococcus aureus* (VRSA), Vancomycin intermediate *Staphylococcus aureus* (VISA), and Vancomycin resistant *Enterococcus* (VRE).

As a result of rising prevalence of MRSA, empiric therapy for hospitalized individuals with ABSSSI usually includes intravenous use of an antimicrobial with activity against MRSA and an agent that has activity for the other possible pathogens. Out-patients may be managed with a cost effective oral agent.

The approach to treatment ASSSSI and pneumonia and antimicrobial selection is guided by manifestation of infection, severity of clinical presentation, location of infection, and results of culture and sensitivities. Other variables to consider in antimicrobial selection include cost, patient risk factors, drug interaction potential, efficacy and safety, monitoring requirements, likely pathogens, and local resistance patterns.

An adequate clinical specimen should be obtained prior to the start of treatment for culture, gram stain, and *in vitro* susceptibility testing. This is an important step for describing the underlying bacterial etiology of the infection. Once these results are known, it may be possible to narrow or change empiric antimicrobial therapy to one that is more cost effective and one that has specific activity for the particular micro-organism present. Depending upon agent chosen, this may allow for transition from intravenous to oral therapy to facilitate discharge to home for hospitalized individuals who are clinically stable to do so.

Numerous antimicrobials are available for treatment of ABSSSI that have activity against gram positive bacteria (including MRSA) as well as the some of the other pathogens involved in the infection. These include Vancomycin (IV, generic), Daptomycin IV (Cubicin), Dalbavacin IV (Dalavance), Oritavancin IV (Orbactiv), Telavancin IV (Vibativ), Ceftaroline IV (Teflaro), Tigecycline IV (Tygacil), Doxycycline (IV and PO, generic), Minocycline (IV and PO), Clindamycin (IV and PO, generic), Trimethoprim-Sulfamethoxazole (IV and PO, generic), Linezolid IV and PO (Zyvox), and Tedizolid IV and PO (Sivextro).

Other antimicrobial agents used for pneumonia can include Amoxicillin + Clavulanate, Cephalosporins, Fluoroquinolone (Levofloxacin, Gemifloxacin, Moxifloxacin, Ofloxacin), Clindamycin, Trimethoprim-sulfamethoxazole, Doxycycline, Minocycline, and Macrolide (Azithromycin, Erythromycin, Clarithromycin).

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Both Tedizolid and Linezolid can be administered orally or intravenously. A short 6-day course of Tedizolid has been shown to be statistically non-inferior to a 10-day course of Linezolid for both early and sustained clinical responses in patients with ABSSSIs.

Definitions:

Acute bacterial skin and skin structure infection (ABSSSI):

A bacterial infection of the skin with a lesion size area of at least 75 cm^2 (measured by the area of redness, edema, or induration).

The following infections are defined as ABSSSIs:

Cellulitis/erysipelas: a diffuse skin infection characterized by spreading areas of redness, edema, and/or induration

Wound infection: an infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration

Major cutaneous abscess: an infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration

Spectrum of Activity:

Sivextro (tedizolid):

Activity against the following, shown by *in vitro* and clinical infections:

Enterococcus faecalis
Staphylococcus aureus (includes methicillin resistant (MRSA) & methicillin susceptible (MSSA) isolates)
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus intermedius
Streptococcus constellatus
Streptococcus pyogenes

Zyvox (linezolid):

Activity against the following, shown by *in vitro* and clinical infections:

Enterococcus faecium (Vancomycin resistant isolates only)
Staphylococcus aureus (includes MRSA isolates)
Streptococcus agalactiae
Streptococcus pneumonia
Streptococcus pyogenes

Other potential oral anti-microbial therapy for ABSSSI or Pneumonia (dependent on manifestation of infection, severity and location of infection, and results of culture and sensitivities):

Amoxicillin + Clavulanate

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Dicloxacillin
Cephalosporin
Fluoroquinolone (Levofloxacin, Gemifloxacin, Moxifloxacin, Ofloxacin)
Clindamycin
Trimethoprim-sulfamethoxazole
Doxycycline
Minocycline
Macrolide (Azithromycin, Erythromycin, Clarithromycin)

Resources:

Sivextro (tedizolid) product information, revised by Merck Sharp & Dohme Corp. 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 07, 2021.

Zyvox (linezolid) product information, revised by Pharmacia & Upjohn Company LLC. 04-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 07, 2021.

Linezolid powder for suspension product information, revised by West-Ward Pharmaceuticals Corp. 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 07, 2021.

Linezolid tablet product information, revised by Amneal Pharmaceuticals LLC. 09-2020. Available at at DailyMed http://dailymed.nlm.nih.gov. Accessed September 07, 2021.

Spelman D, Baddour LM. Cellulitis and skin abscess in adults: Treatment. In: UpToDate, Lowry FD, Baron EL (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 07, 2021.

Lowry FD. Methicillin-resistant Staphylococcus aureus (MRSA) in adults: Treatment of skin and soft tissue infections. In: UpToDate, Spelman D, Baron L (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 07, 2021.

Lowry FD. Methicillin-resistant Staphylococcus aureus (MRSA) in adults: Treatment of bacteremia. In: UpToDate, Spelman D, Baron L (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 07, 2021.

Ramirez JA. Overview of community-acquired pneumonia in adults. In: UpToDate, File TM, Bond S (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 07, 2021.

File TM. Treatment of community-acquired pneumonia in adults in the outpatient setting. In: UpToDate, Ramirez JA, Bond S (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 07, 2021.

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Klompas M. Treatment of hospital-acquired and ventilator-associated pneumonia in adults. In: UpToDate, File TM, Bond S (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 07, 2021.