BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 11/20/14**
SECTION: DRUGS	**LAST REVIEW DATE: 11/16/17**
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	ARCHIVE DATE:

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

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

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.

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.

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ZYVOX® (linezolid) oral suspension and tablet (cont.)

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).

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:

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 pyogenes
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus intermedius
Streptococcus constellatus

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Activity against the following, shown by *in vitro* data:
Enterococcus faecium
Staphylococcus epidermidis [includes methicillin resistant (MRSE) & methicillin susceptible (MSSE)]
Staphylococcus haemolyticus
Staphylococcus lugdunensis
Streptococcus pneumonia

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 pyogenes
Streptococcus agalactiae
Streptococcus pneumonia

Activity against the following, shown by *in vitro* data:
Enterococcus faecalis (includes Vancomycin resistant isolates)
Enterococcus faecium (Vancomycin susceptible isolates)
Staphylococcus epidermidis (includes MRSE isolates)
Staphylococcus haemolyticus
Viridans group streptococci
Pasturella multocida

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

SIVEXTRO™ (tedizolid phosphate) oral tablet
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Sivextro (tedizolid phosphate)

Medication class:
Anti-Infective Agents - Oxazolidinones

FDA-approved indication(s):
- An oxazolidinone-class antibacterial drug indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria.
  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 or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Recommended Dose:
- 200 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour for six (6) days.

Available Dosage Forms:
- Tablet: 200 mg
- For injection: 200 mg, sterile, lyophilized powder in single-use vial for reconstitution for intravenous infusion

Warnings and Precautions:
- Patients with neutropenia: The safety and efficacy of Sivextro in patients with neutropenia (neutrophil counts <1000 cells/mm^3) have not been adequately evaluated. In an animal model of infection, the antibacterial activity of Sivextro was reduced in the absence of granulocytes. Consider alternative therapies in neutropenic patients.
- *Clostridium difficile*-associated diarrhea: Evaluate if diarrhea occurs.

Zyvox (linezolid)

Medication class:
Anti-Infective Agents - Oxazolidinones

FDA-approved indication(s):
- An oxazolidinone-class antibacterial 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;
  - Vancomycin-resistant *Enterococcus faecium* infections.

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

Recommended Dose:

	Dosage, Route, and Frequency of Administration		
Infection	Pediatric Patients	Adults and Adolescents	Duration (days)
Nosocomial pneumonia Community-acquired pneumonia, including concurrent bacteremia Complicated skin and skin structure infections	10 mg/kg intravenous or oral every 8 hours	600 mg intravenous or oral every 12 hours	10 to 14
Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia	10 mg/kg intravenous or oral every 8 hours	600 mg intravenous or oral every 12 hours	14 to 28
Uncomplicated skin and skin structure infections	less than 5 yrs: 10 mg/kg oral every 8 hours 5–11 yrs: 10 mg/kg oral every 12 hours	Adults: 400 mg oral every 12 hours Adolescents: 600 mg oral every 12 hours	10 to 14

Available Dosage Forms:
- Injection: 200, 400, 600 mg linezolid
- Tablet: 600 mg linezolid
- Oral Suspension: 100 mg of linezolid per each 5 mL

Warnings and Precautions:
- Myelosuppression: Monitor complete blood counts weekly. Consider discontinuation in patients who develop or have worsening myelosuppression.
- Peripheral and optic neuropathy: Reported primarily in patients treated for longer than 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.
- Serotonin syndrome: Patients taking serotonergic antidepressants should receive Zyvox only if no other therapies are available. Discontinue serotonergic antidepressants and monitor patients for signs and symptoms of both serotonin syndrome and antidepressant discontinuation.
- A mortality imbalance was seen in an investigational study in linezolid-treated patients with catheter-related bloodstream infections.
- *Clostridium difficile* associated diarrhea: Evaluate if diarrhea occurs.
- Potential interactions producing elevation of blood pressure: monitor blood pressure.
- Hypoglycemia: Postmarketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents.

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Criteria:

- **Criteria for initial therapy:** Sivextro or Zyvox is considered ***medically necessary*** for the treatment infections caused by susceptible bacteria with medical record documentation of **ALL** of the following:

1. Diagnosis is **ONE** of the following:
   - **For Sivextro**: proven or strongly suspected acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible bacteria for individuals 18 years of age or older
   - **For Zyvox**: proven or strongly suspected clinical infection caused by susceptible bacteria per manufacturer label
   - When applicable, individual is transitioning intravenous therapy to oral therapy to facilitate a hospital discharge

2. Culture was obtained from **ONE** of the following:
   - **For Sivextro**: skin or skin structure (not from sputum, blood, or other site)
   - **For Zyvox**: skin, skin structure, blood, or sputum

3. Proven or strongly suspected micro-organism is **ONE** of the following:
   - Methicillin resistant *Staphylococcus aureus* (MRSA)
   - Methicillin resistant *Staphylococcus epidermidis* (MRSE)
   - *Enterococcus faecalis* (Vancomycin resistant)
   - *Enterococcus faecium* (Vancomycin resistant)
   - Vancomycin intermediate *Staphylococcus aureus* (VISA)
   - Vancomycin resistant *Staphylococcus aureus* (VRSA)

4. Individual has failure, contraindication, or intolerance to linezolid

5. Absence of **ALL** of the following contraindications:
   - **For Zyvox**:
     - Known hypersensitivity to linezolid or any of the other components of the product
     - Use with or within two weeks of a mono-amine oxidase inhibitor (MAOI)
   - **For Sivextro:**
     - Use in a patient on an MAOI
     - Use in a patient taking serotonergic agents including serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone

Initial approval duration: Up to 6 weeks at 2 tablets per day
IV infusion or injections – MEDICAL BENEFIT ONLY

Resources:

Sivextro package insert. Revised by manufacturer on 08-2017. Accessed on 10-26-17.

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Zyvox package insert. Revised by manufacturer on 05-2017. Accessed on 10-26-17.

Linezolid package insert. Revised by manufacturer on 03-2016. Reviewed on 07-10-2017

Sivextro package insert. Revised by manufacturer on 10-2016. Reviewed on 07-10-2017

Sivextro. Package Insert. Revised by manufacturer 07/2015. Accessed 05-23-2016.

Sivextro. Package Insert. Reference ID 3529436. Revised by manufacturer 06/2014. Accessed 10-22-2014.

Zyvox. Package Insert. Revised by manufacturer 07/2015. Accessed 05-23-2016.

Zyvox. Package Insert. Reference ID 3441619. Revised by manufacturer 09/2013. Accessed 10-22-2014.

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 Disease Society of America. CID 2014 DOI: 10.1093/cid/ciu296

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.