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Section:	Prescription Drugs	**Effective Date:**	July 1, 2023
Subsection:	Anti-infective Agents	**Original Policy Date:**	December 7, 2011
Subject:	Zyvox	**Page:**	1 of 7

Last Review Date: June 15, 2023

Zyvox

Description

Zyvox (linezolid)

Background
Zyvox is an oxazolidinone, which is a class of synthetic antibiotics. Unlike other antibiotics Zyvox inhibits bacterial translation by binding to bacterial 23S ribosomal RNA, which blocks the formation of the functional 70S initiation complex. This unique mechanism of action lessens the likelihood of resistance with other classes of antibiotics. Zyvox is bacteriostatic or bactericidal depending on the bacterial strain (1).

Regulatory Status
FDA-approved indications: (1)
Zyvox is an oxazolidinone-class antibacterial indicated in adults and children for the treatment of the following infections caused by susceptible Gram-positive bacteria:

1. Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]).
2. Community-acquired pneumonia caused by *Streptococcus pneumoniae* (including multi-drug resistant streptococcus pneumoniae [MDRSP] strains), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).
3. Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Zyvox

has not been studied in the treatment of decubitus ulcers.
4. Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*.
5. 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 or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria (1).

The safety and efficacy of Zyvox formulations given for longer than 28 days have not been evaluated in controlled clinical trials (1).

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving Zyvox. Complete blood counts should be monitored weekly in patients who receive Zyvox, particularly in those who are taking for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with Zyvox should be considered in patients who develop or have worsening myelosuppression (1).

Zyvox has the potential to increase blood pressure. Unless patients are monitored for potential increases in blood pressure, Zyvox should not be administered to patients with uncontrolled hypertension, pheochromocytoma, or thyrotoxicosis (1).

Zyvox may cause lactic acidosis, peripheral and optic neuropathy, convulsions, symptomatic hypoglycemia, and *Clostridium difficile* associated diarrhea (1).

Zyvox acts as a monoamine oxidase inhibitor (MAOI) giving it the potential for serotonergic and adrenergic interactions and may cause serotonin syndrome. Spontaneous reports of serotonin syndrome including fatal cases associated with the co-administration of Zyvox and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) (1).

Zyvox is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. An imbalance in mortality was seen in patients treated with Zyvox relative to vancomycin/dicloxacillin/oxacillin in an open-label study in seriously ill patients with intravascular catheter-related infections (1).

Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) Zyvox concentrations following single and multiple dosing of Zyvox; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of Zyvox for the empiric treatment of pediatric patients with central nervous system infections is not recommended (1).

Off-Label Uses:
Zyvox has shown to be effective for pneumonia in patients with cystic fibrosis (CF), which is known to increase risk of serious, difficult to treat respiratory infections. Clinical guidelines for CF recommend aggressive treatment, with Zyvox being one effective agent (2-3).

There is also evidence for Zyvox use in mycobacterial infections. In addition to gram-positive and actinomycotic coverage, in-vitro and clinical case studies report success treating numerous mycobacteria species. This includes common strains M. kansasii and M. tuberculosis (also including multi-drug resistant (MDR-TB)) which show susceptibility. As with other uses, patients should be monitored for side effects (4-8).

Related policies
Baxdela, Nuzyra, Xenleta, Sivextro

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Zyvox may be considered **medically necessary** if the conditions indicated below are met.

Zyvox may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have an infection caused by **OR** strongly suspected to be caused by **ONE** of the following:

1. Vancomycin-Resistant *Entercoccus faecium* infection

2. Nosocomial pneumonia
   Staphylococcus aureus (methicillin-susceptible)
   Staphylococcus aureus (methicillin-resistant)
   Streptococcus pneumoniae (including MDRSP)

3. Community-acquired pneumonia
   Staphylococcus aureus (methicillin-susceptible)
   Streptococcus pneumoniae (including MDRSP)

4. Complicated skin and skin structure infections
   Staphylococcus aureus (methicillin-susceptible)
   Staphylococcus aureus (methicillin-resistant)
   Streptococcus pyogenes
   Streptococcus agalactiae

5. Uncomplicated skin and skin structure infections
   Staphylococcus aureus (methicillin-susceptible)
   Streptococcus pyogenes

6. Actinomycotic unspecified infections
   Inadequate response or intolerance to prior penicillin, tetracycline, erythromycin, clindamycin, chloramphenical, and/or cephalosporins.

7. Nocardiosis Unspecified

8. Actinomycetoma
   Nocardia Asteroides
   Nocardia Brasiliensis
   Nocardia Farcinica
   Nocardia Nova
   Nocardia Transvalensis
   Nocardia Otitidiscaviarum

9. Mycobacterium after failure or intolerance to prior macrolide therapy

10. Pulmonary exacerbations / pneumonia in Cystic Fibrosis (CF) patients

Prior – Approval *Renewal* Requirements
Same as above

Policy Guidelines

Pre - PA Allowance

Quantity 14 day supply every 365 days

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits
Same as above

Rationale

Summary

Zyvox is an oxazolidinone, which is a class of synthetic antibiotics. 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 susceptible bacteria. Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving Zyvox. Zyvox acts as a monoamine oxidase inhibitor (MAOI) and may cause serotonin syndrome. Unless patients are monitored for potential increases in blood pressure, Zyvox should not be administered to patients with uncontrolled hypertension, pheochromocytoma, or thyrotoxicosis. Zyvox is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. Zyvox may cause lactic acidosis, peripheral and optic neuropathy, convulsions, symptomatic hypoglycemia, and *Clostridium difficile* associated diarrhea (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Zyvox while maintaining optimal therapeutic outcomes.

References

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4. Smego RA, Foglia G. Actinomycosis. *Clin Infect Dis*.1998;26:1255-1263.
5. Cavusoglu C, Soyler I, Akinci P. Activities of Linezolid against nontuberculous Mycobacteria. *New Microbiol*.2007;30:411-414.
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8. Park JS. Recent Advances in Tuberculosis and Nontuberculous Mycobacteria Lung Disease. *Tuberc Respir* Dis.2013;74:251-255.

Policy History

Date	Action
February 2007	Removal of the age requirement will accurately reflect the updated package insert labeling for Zyvox which details recommended dosing for patients from birth through 11 years of age and for patients 12 years of age and older.
January 2010	*Pseudomonas pneumonia* was removed from the criteria since it is not FDA approved and there is no clinical literature to support its use.
December 2012	Annual editorial review and update

March 2014	Annual editorial review and reference update Addition of pulmonary exacerbations / pneumonia in Cystic Fibrosis (CF) patients (2,3) Addition to Actinomycotic unspecified infections that patient must have failure or intolerance to prior penicillin, tetracycline, erythromycin, clindamycin, chloramphenicol and/or cephalosporins (4) Addition of *Mycobacterium tuberculosis, Mycobacterium kansasii, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium mucogenicum, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium abscessus Mycobacterium gordonae, Mycobacterium ulcerans,* and *Mycobacterium massiliense* (5-11)
December 2014	Annual editorial review and reference update Removal of the Mycobacterium examples
December 2015	Annual review and reference update
March 2015	Annual editorial review and reference update Policy code changed from 5.03.20 to 5.01.20
December 2017	Annual editorial review and reference update
November 2018	Annual review and reference update
December 2019	Annual review
March 2020	Annual review. Revised requirement to “Patient must have an infection caused by OR strongly suspected to be caused by ONE of the following” per SME
December 2021	Annual review and reference update
December 2022	Annual review and reference update. Changed policy number to 5.01.020
June 2023	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 15, 2023 and is effective on July 1, 2023.