Pharmacy Policy Bulletin

Title:	Oral Anti-infective Agents
Policy #:	Rx.01.66

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product lin may be subject to precertification, age, gender or quantity restrictions. Individual member benefits must be verif

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the tim that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration route changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when consid updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **azithromycin (ZMax®) bedaquiline (Sirturo®) germafloxacin (Factive®), isavuconazonium (Cresemba®) linezolid (Zyvox®), posaconazol tedizolid (Sivextro)** as provided under the member's pharmacy benefit.

Description:

AZITHROMYCIN (ZMAX®)

Azithromycin (Zmax®) is indicated for the treatment of mild-to-moderate infections that are caused by susceptible strains specific conditions such as: acute bacterial sinusitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococc pneumonia due to Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, or Streptococcus pneum

Azithromycin (Zmax®) is an extended-release formulation using microsphere technology to provide a complete course of Azithromycin (Zmax®) is similar to other azithromycin-containing drugs that inhibit protein synthesis by binding at the 50 S

BEDAQUILINE (SIRTURO®)

Bedaquiline (Sirturo®) is indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resista for use when an effective treatment regimen cannot otherwise be provided.

Bedaquiline (Sirturo®) is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP synthase, an enzyme th Mycobacterium tuberculosis.

GEMIFLOXACIN (FACTIVE®)

Gemifloxacin (Factive®) is indicated for the treatment of infections caused by susceptible strains of the designated microo acute bacterial exacerbation of chronic bronchitis and mild to moderate community-acquired pneumonia.

Gemifloxacin (Factive®) acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV bacterial growth.

ISAVUCONAZONIUM (CRESEMBA®)

Isavuconazonium (Cresemba®) is indicated for the treatment of invasive aspergillosis and invasive mucormycosis.

Isavuconazonium (Cresemba®) is the prodrug of isavuconazole, an azole antifungal. Isavuconazole inhibits the synthesis fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase. T conversion of lanosterol to ergosterol. An accumulation of methylated sterol precursors and a depletion of ergosterol withi

membrane structure and function.

LINEZOLID (ZYVOX®)
Linezolid (Zyvox®) formulations are indicated for the treatment of the following infections that are caused by susceptible s

- Vancomycin-resistant Enterococcus faecium infections, including cases with concurrent bacteremia.
- Nosocomial pneumonia caused by Staphylococcus aureus (methicillin-susceptible and -resistant strains) or Strep strains only). Combination therapy may be clinically indicated if the documented or presumptive pathogens includ
- Complicated skin and skin structure infections, including diabetic foot infections without concomitant osteomyelitis (methicillin-susceptible and -resistant strains), Streptococcus pyogenes, or Streptococcus agalactiae. Linezolid (Z treatment of diabetic foot and decubitus ulcers. Combination therapy may be clinically indicated if the documented negative organisms.
- Uncomplicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible strain
- Community-acquired pneumonia caused by Streptococcus pneumoniae (penicillin-susceptible strains only), includ Staphylococcus aureus (methicillin-susceptible strains only).

Due to concerns about inappropriate use of antibiotics leading to an increase in resistance, providers should carefully con with linezolid (Zyvox®) in the outpatient setting.

Linezolid (Zyvox®) is a synthetic antibacterial agent of the oxazolidinone class. Appropriate specimens for bacteriological and identify the causative organisms and to determine their susceptibility to linezolid (Zyvox®). Therapy may be instituted these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

POSACONAZOLE (NOXAFIL®)
Posaconazole (Noxafil®) is indicated for prophylaxis of invasive Aspergillus and Candida infections in individuals, 13 year developing these infections due to being severely immunocompromised (e.g., hematopoietic stem cell transplant [HSCT] [GVHD] or individuals with hematologic malignancies who have prolonged neutropenia from chemotherapy). Posaconazo oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

Posaconazole (Noxafil®), a triazole antifungal agent, blocks the synthesis of ergosterol, a key component of the fungal ce enzyme lanosterol 14a-demethylase and accumulation of methylated sterol precursors. Posaconazole (Noxafil®) has sho fumigatus and Candida albicans, including C. albicans, isolates from individuals refractory to itraconazole or fluconazole c

TEDIZOLID (SIVEXTRO)
Tedizolid (Sivextro) is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections ca gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *Streptococcus anginosus*, *Streptococcus intermediu* *Enterococcus faecalis.*

Tedizolid (Sivextro) binds to the 50S bacterial ribosomal subunit. This prevents the formation of a functional 70S initiation translation process and subsequently inhibits protein synthesis. Tedizolid is bacteriostatic against enterococci, staphyloco

Policy:

AZITHROMYCIN (ZMAX®)
Azithromycin (Zmax®) is approved when there is documentation of inability to tolerate all other generic formulations of a

BEDAQUILINE (SIRTURO®)
Bedaquiline (Sirturo®) is approved when ALL of the following inclusion criteria are met:

1. Diagnosis of pulmonary multi-drug resistant tuberculosis (MDR-TB); and
2. Member is 18 years of age or older; and
3. Bedequiline is used as combination therapy as defined by ONE of the following:
    a. With at least 3 other drugs to which the member's MDR-TB isolate has been shown to be susceptible
    b. With at least 4 other drugs to which the patient's MDR-TB isolate is likely to be susceptible

4. Recommended by infectious disease specialist or pulmonologist

Authorization length: Bedequiline is authorized for 24 weeks

GEMIFLOXACIN (FACTIVE®)
Gemifloxacin (Factive®) is approved when BOTH of the following inclusion criteria are met:
1. Diagnosis of acute bacterial exacerbation of chronic bronchitis or community-acquired pneumonia; and
2. Documentation of ONE of the following:
    a. Inadequate response or intolerability to generic levofloxacin or generic moxifloxacin; or
    b. Susceptibility results indicating gemifloxacin is the only fluoroquinolone option

ISAVUCONAZONIUM (CRESEMBA®)
Isavuconazonium (Cresemba®) is approved when BOTH of the following are met:
1. Member is 18 years of age or older; and
2. Diagnosis of ONE of the following:
    a. Treatment of invasive aspergillosis after inadequate response to voriconazole); or
    b. Treatment of invasive mucormycosis

LINEZOLID (ZYVOX®)
Linezolid (Zyvox®) is approved when BOTH of the following inclusion criteria are met:
1. Prescribed by an infectious diseases specialist or upon consultation with an infectious disease specialist (tel
2. Current bacterial infection with either
    a. Inadequate response or inability to tolerate ALL antibiotics to which the organism is susceptible; or
    b. Linezolid is the only antibiotic to which the organism is susceptible

Linezolid (Zyvox®) Authorization Length: Linezolid is approved for 28 days [56 tablets or 1680mL] for vancomycin resi
tablets or 840mL) for all other indications.

POSACONAZOLE (NOXAFIL®)
Posaconazole (Noxafil®) is approved when BOTH of the following inclusion criteria are met:
1. Member is 13 years of age or older; and
2. Documentation of ONE of the following
    a. Prophylaxis of invasive Aspergillus and Candida infections due to a severe immunocompromised sta
    b. Treatment of invasive Aspergillus and Candida infections due to a severe immunocompromised state voriconazole (Vfend®); or
    c. Treatment of oropharyngeal candidiasis with inadequate response to both itraconazole and fluconazo

TEDIZOLID (SIVEXTRO)
Tedizolid (Sivextro) is approved when ALL of the following inclusion criteria are met:
1. Documentation of use for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused microorganisms and ONE of the following:
    a. Inadequate response or inability to tolerate ALL antibiotics to which the organism is susceptible
    b. Tedizolid is the only antibiotic to which the organism is susceptible
2. Prescribed by an infectious disease specialist or upon consultation with an infectious disease specialist (telephone consultation is acceptable)

Black Box Warning:

BEDAQUILINE (SIRTURO®)
An increased risk of death was seen in the bedaquiline group (11.4%) compared with the placebo group (2.5%) in 1 place when an effective treatment regimen cannot otherwise be provided.
QT prolongation can occur with bedaquiline. Use with drugs that prolong the QT interval may cause addictive QT prolonga

GEMIFLOXACIN (FACTIVE®)
Fluoroquinolones, including gemifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages older than 60 years; in patients taking corticosteroid drugs; and in patients with kidney, heart, or lung transplants.

Fluoroquinolones, including gemifloxacin, may exacerbate muscle weakness in individuals with myasthenia gravis. Avoid
of myasthenia gravis.

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Blac

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are
the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are
benefit contract exclusions for all products of the Company.

References:

Zyvox® (linezolid). [Zyvox® (linezolid) Web site]. 2010. Available at: http://www.zyvox.com. Accessed June 18, 2014.

Zyvox® (linezolid). [e-facts Drug Facts & Comparisons Web site]. Available at: http://online.factsandcomparisons.com/log
subscription only]. Accessed June 12, 2014.

Noxafil® (Posaconazole) [package insert]. [Noxafil® (Posaconazole) Web site]. Kenilworth, NJ: Schering-Plough; 2010. A
http://www.noxafil.com. Revised 03/2014. Accessed June 13, 2014.

Ahuja SD, Ashkin D, Avendano M, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient O
analysis of 9,153 Patients. PLoS Med. 2012; 9(8):e1001300. doi:10.1371/journal.pmed.1001300.

Al-Dabbagh M, Lapphra K, McGloin R, et al. Drug Resistant Tuberculosis: Pediatric Guidelines. Pediatr Infect Dis J. 2011

American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm R

Briefing Package: NDA 204-384. Sirturo™ (bedaquiline 100 mg tablets) For the treatment of adults (≥ 18 years) as part of
drug resistant tuberculosis (MDRTB).

Division of Anti-Infective Products Office of Antimicrobial Products CDER, FDA. November 28, 2012. Available at:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCom
14, 2013.

Centers for Disease Control and Prevention. Update: adverse event data and revised American Thoracic Society/CDC re
and pyrazinamide for treatment of latent tuberculosis infection-United States, 2003. Morb Mortal Wkly Rep. 2003; 52:735-
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm. Accessed June 12, 2014.

Centers for Disease Prevention and Control (CDC). Basic Tuberculosis Facts. Available at: http://www.cdc.gov/tb/topic/ba

Centers for Disease Prevention and Control (CDC). Reported Tuberculosis in the United States: 2011. Atlanta, GA: U.S. D
CDC, October 2012. Available at: http://www.cdc.gov/tb/statistics/reports/2011/pdf/report2011.pdf. Accessed June 12, 20

Diacon AH, Donald PR, Pym A, et al. Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Mult
Outcome, Tolerability, and Effect on Emergence of Drug Resistance. Antimicrob Agents Chemother. 2012; 56(6):3271-32

Diacon AH, Pym A, Grobusch M, et al. The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis. N Engl J Med.

Falzon D, Jaramillo E, Schünemann HJ, et al. WHO guidelines for the programmatic management of drug-resistant tuberc
38:516–528.

SIRTURO prescribing information. Janssen Therapeutics; Titusville, NJ. December 2012. Revised 10/2013. Accessed Ju

World Health Organization. United States Tuberculosis profile. Available at:
https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCoun

Accessed January 8, 2013.

World Health Organization. The Global Plan to Stop TB Fact Sheet. 2011. Available at: http://www.stoptb.org/assets/documents/global/plan/stopTB2011_insert_FINAL.pdf. Accessed June 12, 2014.

Sivextro Package Insert. Cubist Pharmaceuticals, Lexington, MA, 06/2014.

Cresemba (Isavuconazonium) [package insert]. Northbrook, IL. Astellas Pharma US. April 2015. Available from: http://ww July 13, 2015.

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/re Company policies apply.

Brand Name	Generic Name
Cresemba	isavuconazonium
Factive	gemifloxacin
Noxafil	posaconazole
Sirturo	bedaquiline
Sivextro	tedizolid
Zmax	azithromycin
Zyvox	linezolid

Cross References:

Policy Version Number:	8.00
P&T Approval Date:	July 09, 2015
Policy Effective Date:	September 01, 2015
Next Required Review Date:	July 09, 2016