

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 line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be 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 **bedaquiline (Sirturo®)**, **delafloxacin (Baxdela®)**, **germafloxacin (Factive®)**, **isavuconazonium (Cresemba®)**, **linezolid (Zyvox®)**, **posaconazole (Noxafil®)**, and **tedizolid (Sivextro®)** as provided under the member's prescription drug benefit.

▸ Description:

BEDAQUILINE (SIRTURO®)

Bedaquiline (Sirturo®) is indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve Sirturo® 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 that is essential for the generation of energy in *Mycobacterium tuberculosis*.

DELAFLOXACIN (BAXDELA®)

Delafloxacin (BAXDELA®) is a fluoroquinolone antibacterial indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria:

- Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis*.

- Gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Delafloxacin (BAXDELA®) belongs to the fluoroquinolone class of antibacterial drugs and is anionic in nature. The antibacterial activity of delafloxacin is due to the inhibition of both bacterial topoisomerase IV and DNA gyrase (topoisomerase II) enzymes which are required for bacterial DNA replication, transcription, repair, and recombination. Delafloxacin exhibits a concentration-dependent bactericidal activity against gram-positive and gram-negative bacteria in vitro.

GEMIFLOXACIN (FACTIVE®)

Gemifloxacin (Factive®) is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in specific conditions such as: 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 (TOPO IV), which are essential for 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 of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase. This enzyme is responsible for the conversion of lanosterol to ergosterol. An accumulation of methylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakens the membrane structure and function.

LINEZOLID (ZYVOX®)

Linezolid (Zyvox®) formulations are indicated for the treatment of the following infections that are caused by susceptible strains of the designated micro-organisms:

- Vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.
- Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pneumoniae* (penicillin-susceptible strains only). Combination therapy may be clinically indicated if the documented or presumptive pathogens include gram-negative organisms.
- 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*. Linezolid (Zyvox®) has not been studied in the treatment of diabetic foot and decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include gram-negative organisms.
- Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.
- Community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia or *Staphylococcus aureus* (methicillin-susceptible strains only).

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

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

POSACONAZOLE (NOXAFIL®)

Posaconazole (Noxafil®) injection, delayed-release tablets, and oral suspension, are indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, who are at high risk of developing these infections due to being severely immunocompromised (e.g., hematopoietic stem cell transplant [HSCT] recipients with graft-versus-host disease [GVHD] or individuals with hematologic malignancies who have prolonged neutropenia from chemotherapy). Noxafil injection is indicated in patients 18 years of age and older. Noxafil delayed-release tablets and oral suspension are indicated in patients 13 years of age and older.

Posaconazole (Noxafil®) is indicated for the treatment of 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 cell membrane, through the inhibition of the enzyme lanosterol 14α-demethylase and accumulation of methylated sterol precursors. Posaconazole (Noxafil®) has shown in vitro activity against *Aspergillus fumigatus* and *Candida albicans*, including *C. albicans*, isolates from individuals refractory to itraconazole or fluconazole or both drugs.

TEDIZOLID (SIVEXTRO®)

Tedizolid (Sivextro®) is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections 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*.

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

Policy:

BEDAQUILINE (SIRTURO®)

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

- A. Diagnosis of pulmonary multi-drug resistant tuberculosis (MDR-TB), for which an effective treatment regimen cannot otherwise be established; and
- B. Member is 18 years of age or older; and
- C. Recommended by an infection disease specialist or pulmonologists; and
- D. Bedaquiline is used as combination therapy as defined by ONE of the following:

1. With at least 3 other drugs to which the member's MDR-TB isolate has been shown to be susceptible in vitro; or
2. With at least 4 other drugs to which the patient's MDR-TB isolate is likely to be susceptible

Authorization length: Bedaquiline is authorized for 24 weeks

GEMIFLOXACIN (FACTIVE®)

Gemifloxacin (Factive®) is approved when BOTH of the following inclusion criteria are met:

- A. Diagnosis of acute bacterial exacerbation of chronic bronchitis or community-acquired pneumonia; and
- B. Documentation of ONE of the following:
 1. Inadequate response or intolerability to generic levofloxacin or generic moxifloxacin; or
 2. Susceptibility results indicating gemifloxacin is the only fluoroquinolone option

ISAVUCONAZONIUM (CRESEMBA®)

Isavuconazonium (Cresemba®) is approved when ALL of the following are met:

- A. Member is 18 years of age or older; and
- B. Prescribed by an infectious diseases specialist or upon consultation with an infectious disease specialist (telephone consultation is acceptable); and
- C. Diagnosis of ONE of the following:
 1. Treatment of invasive aspergillosis and inadequate response or inability to tolerate voriconazole; or
 2. Treatment of invasive mucormycosis

DELAFLOXACIN (BAXDELA®) or LINEZOLID (ZYVOX®)

Delafloxacin (Baxdela®) or Linezolid (Zyvox®) is approved when BOTH of the following inclusion criteria are met:

- A. Prescribed by an infectious diseases specialist or upon consultation with an infectious disease specialist (telephone consultation is acceptable); and
- B. Current bacterial infection with either
 1. Inadequate response or inability to tolerate ALL antibiotics to which the organism is susceptible; or
 2. Linezolid is the only antibiotic to which the organism is susceptible

Delafloxacin (Baxdela®) Authorization length: Delafloxacin is approved for 14 days (28 tablets).

Linezolid (Zyvox®) Authorization Length: Linezolid is approved for 28 days [56 tablets or 1680mL] for vancomycin resistant enterococcus faecium or 14-days [28 tablets or 840mL] for all other indications.

POSACONAZOLE (NOXAFIL®)

Posaconazole (Noxafil®) is approved when BOTH of the following inclusion criteria are met:

- A. Member is 13 years of age or older; and
- B. Documentation of ONE of the following
 1. Prophylaxis of invasive Aspergillus and Candida infections due to a severe immunocompromised state; or
 2. Treatment of invasive Aspergillus and Candida infections due to a severe immunocompromised state after inadequate response to voriconazole (Vfend®); or

3. Treatment of oropharyngeal candidiasis with inadequate response to both itraconazole and fluconazole

TEDIZOLID (SIVEXTRO®)

Tedizolid (Sivextro®) is approved when ALL of the following inclusion criteria are met:

- A. Member is 18 years of age or older; and
- B. Prescribed by an infectious disease specialist or upon consultation with an infectious disease specialist (telephone consultation is acceptable); and
- C. Documentation of use for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of Gram-positive microorganisms and ONE of the following:
 1. Inadequate response or inability to tolerate ALL antibiotics to which the organism is susceptible; or
 2. Tedizolid is the only antibiotic to which the organism is susceptible

▶ Black Box Warning as shown in the drug Prescribing Information:

BEDAQUILINE (SIRTURO®)

An increased risk of death was seen in the bedaquiline group (11.4%) compared with the placebo group (2.5%) in 1 placebo-controlled trial. Only use bedaquiline 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 additive QT prolongation.

DELAFLOXACIN (BAXDELA®)

Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects. Discontinue delafloxacin immediately and avoid the use of fluoroquinolones, including delafloxacin, in patients who experience any of these serious adverse reactions.

Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid delafloxacin in patients with known history of myasthenia gravis.

GEMIFLOXACIN (FACTIVE®)

Fluoroquinolones, including gemifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in patients older than 60 years; in patients taking corticosteroid drugs; and in patients with kidney, heart, or lung transplants. Fluoroquinolones, including gemifloxacin, are associated with disabling and potentially irreversible serious side effects, such as peripheral neuropathy and central nervous system effects. Discontinue gemifloxacin immediately and avoid use of fluoroquinolones, including gemifloxacin, in patients who experience any of these serious adverse reactions

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

Because fluoroquinolones, including gemifloxacin, have been associated with serious adverse reactions, reserve gemifloxacin for use in patients who have no alternative treatment options for acute bacterial exacerbation of chronic bronchitis.

▸ Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

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

▸ References:

Baxdela® (delafloxacin) [package insert]. Lincolnshire, IL. Melinta Therapeutics, Inc. October 2018. Available at: <https://baxdela.com/docs/baxdela-prescribing-information.pdf> Accessed February 18, 2019.

Cresemba® (isavuconazonium) [package insert]. Northbrook, IL. Astellas Pharma US. April 2018. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=8f7f73b8-586a-4df0-935f-fecd4696c16c&type=display>. Accessed February 18, 2019.

Factive® (gemifloxacin) [package insert]. Toronto, Canada. Merus Labs. May 2016. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=63f60426-e27f-4258-9bfc-b4a15ebdca83&type=display>. Accessed February 18, 2019.

Noxafil® (posaconazole) [package insert]. White House Station, NJ: Merc and Co, Inc. September 2017. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=b073b082-7b57-4423-8c06-4fd4263d6f84&type=display>. Accessed February 18, 2019

Sirturo® (bedaquiline) [package insert]. Janssen Therapeutics; Titusville, NJ. October 2018. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=1534c9ae-4948-4cf4-9f66-222a99db6d0e&type=display>. Accessed February 18, 2019.

Sivextro® (tidizolid) [package insert]. White House Station, NJ: Merc and Co, Inc. August 2017. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=75672079-589f-451a-bdbf-eaebcfcc80a9&type=display>. Accessed February 18, 2019.

Zyvox® (linezolid) [package insert]. New York, NY. Pfizer. July 2018. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=649>. Accessed February 18, 2019.

▸ Applicable Drugs:

i Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name	Generic Name
Baxdela®	delafloxacin
Cresemba®	isavuconazonium
Factive®	gemifloxacin
Noxafil®	posaconazole
Sirturo®	bedaquiline
Sivextro®	tedizolid
Zyvox®	linezolid

▸ Cross References:

N/A

Policy Version Number:	13.00
P&T Approval Date:	January 10, 2019
Policy Effective Date:	April 01, 2019
Next Required Review Date:	January 10, 2020

The Policy Bulletins on this web site were developed to assist the Company in administering the provisions of the respective benefit programs, and do not constitute a contract. If you have coverage through the Company, please refer to your specific benefit program for the terms, conditions, limitations and exclusions of your coverage. Company does not provide health care services, medical advice or treatment, or guarantee the outcome or results of any medical services/treatments. The facility and professional providers are responsible for providing medical advice and treatment. Facility and professional providers are independent contractors and are not employees or agents of the Company. If you have a specific medical condition, please consult with your doctor. The Company reserves the right at any time to change or update its Policy Bulletins.