BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES		**ORIGINAL EFFECTIVE DATE:**	**2/13/2020**
SECTION:	**DRUGS**	**LAST REVIEW DATE:**	**5/20/2021**
		LAST CRITERIA REVISION DATE:	**5/20/2021**
		ARCHIVE DATE:	

CYCLOSERINE
PRETOMANID
SIRTURO® (bedaquiline)

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.**

CYCLOSERINE
PRETOMANID
SIRTURO® (bedaquiline)

Cycloserine

Criteria:

- **Criteria for therapy:** Cycloserine 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 a Pulmonologist or Infectious Disease Specialist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of active pulmonary or extra-pulmonary tuberculosis (including renal disease) where the causative organism is susceptible to cycloserine

  4. Use is to be supervised by and undertaken by the appropriate state or local agency Tuberculosis Clinic responsible for a directly observed therapy (DOT)

  5. Use is with a combination regimen of other drugs with known susceptibility for tuberculosis

  6. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Culture and sensitivity report shows susceptibility to cycloserine
     b. Susceptibility to the other anti-tuberculosis agents in regimen

  7. There are **NO** contraindications. Contraindications include:
     a. Epilepsy
     b. Severe renal insufficiency
     c. Excessive concurrent use of alcohol
     d. Depression
     e. Severe anxiety
     f. Psychosis

  Approval duration:
  1-month supply, individual to be directed to appropriate state or local agency responsible for DOT
  Will not be renewed

- 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**

CYCLOSERINE
PRETOMANID
SIRTURO® (bedaquiline)

Pretomanid

Criteria:

- **Criteria for therapy:** Pretomanid 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 an Infectious Disease Specialist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of pulmonary tuberculosis (TB) that is **ONE** of the following:
    a. Extensive drug resistant (XDR TB)
    b. Treatment-intolerant multi-drug resistant (TI-MDR TB)
    c. Nonresponsive multi-drug resistant (NR-MDR TB)

4. Use is to be supervised by and undertaken by the appropriate state or local agency Tuberculosis Clinic responsible for a directly observed therapy (DOT)

5. Use is with a combination regimen of Pretomanid, Sirturo (bedaquiline), and linezolid (brand Zyvox or generic)

6. Individual does not have **ANY** of the following conditions:
    a. Drug-sensitive (DS) tuberculosis
    b. Latent infection due to *Mycobacterium tuberculosis*
    c. Extra-pulmonary infection due to *Mycobacterium tuberculosis*
    d. MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy
    e. Hepatic impairment
    f. Renal impairment

7. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Alanine aminotransferase
    b. Aspartate aminotransferase
    c. Alkaline phosphatase
    d. Bilirubin
    e. Serum potassium, calcium, and magnesium, correct if abnormal
    f. Electrocardiogram (ECG)

8. There are no contraindications to the use of linezolid (brand Zyvox or generic) or Sirturo (bedaquiline)

CYCLOSERINE
PRETOMANID
SIRTURO® (bedaquiline)

Approval duration:
1-month supply, individual to be directed to appropriate state or local agency responsible for DOT
Will not be renewed

- 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**

Sirturo (bedaquiline)

Criteria:

- **Criteria for therapy:** Sirturo (bedaquiline) 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 an Infectious Disease Specialist
2. Individual is 5 years of age or older and weighs at least 15 kg
3. A confirmed diagnosis pulmonary multi-drug resistant (MDR) tuberculosis (TB)
4. Use is to be supervised by and undertaken by the appropriate state or local agency Tuberculosis Clinic responsible for a directly observed therapy (DOT)
5. Use is with a combination regimen with at least 3 other drugs to which the individual's MDR TB is shown to be susceptible or with at least 4 other drugs to which the individual's MDR TB is likely to be susceptible
6. Individual does not have **ANY** of the following conditions:
    a. Drug-sensitive (DS) tuberculosis;
    b. Latent infection due to *Mycobacterium tuberculosis;*
    c. Extra-pulmonary tuberculosis infections caused by non-tuberculous mycobacteria
    d. HIV infected individual with MDR TB
7. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Electrocardiogram (ECG)
    b. Assessment for signs and symptoms of liver disease

c. Serum potassium, calcium, and magnesium and correct if abnormal
d. Alanine aminotransferase
e. Aspartate aminotransferase
f. Alkaline phosphatase
g. Bilirubin

Initial approval duration:
1-month supply, individual to be directed to appropriate state or local agency responsible for DOT
Will not be renewed

- 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:

Cycloserine is a broad spectrum antibiotic, indicated in the treatment of active pulmonary and extra-pulmonary tuberculosis (including renal disease) when the causative organisms are susceptible to this drug and when treatment with the primary medications (streptomycin, isoniazid, rifampin, and ethambutol) has proved to be inadequate. Like all anti-tuberculosis drugs, it should be administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent. Cycloserine has been shown to be active against most isolates of *Mycobacterium tuberculosis*.

Pretomanid is indicated, as part of a combination regimen with Sirturo (bedaquiline) and linezolid (brand Zyvox or generic) for the treatment of adults with pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Pretomanid Tablets must be used only in combination with Sirturo (bedaquiline) and linezolid (brand Zyvox or generic) as part of the recommended dosing regimen and is administered by directly observed therapy (DOT).

The safety and effectiveness of Pretomanid have not been established for its use in combination with drugs other than Sirturo (bedaquiline) and linezolid (brand Zyvox or generic) as part of the recommended dosing regimen in a limited and specific population of patients. Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients.

Pretomanid is **not indicated** in patients with the following conditions: drug-sensitive (DS) tuberculosis; latent infection due to *Mycobacterium tuberculosis;* extra-pulmonary infection due to *Mycobacterium tuberculosis;* and MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy.

CYCLOSERINE
PRETOMANID
SIRTURO® (bedaquiline)

Sirturo (bedaquiline) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adult and pediatric patients (5 years of age and weighing at least 15 kg) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve Sirturo (bedaquiline) for use when an effective treatment regimen cannot otherwise be provided. Sirturo (bedaquiline) is used only in combination with other antimycobacterial agents and is administered by directly observed therapy (DOT). This indication is approved under accelerated approval based on time to sputum culture conversion. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Only use Sirturo (bedaquiline) in combination with at least 3 other drugs to which the patient's MDR-TB isolate has been shown to be susceptible *in vitro*. If *in vitro* testing results are unavailable, Sirturo (bedaquiline) treatment may be initiated in combination with at least 4 other drugs to which the patient's MDR-TB isolate is likely to be susceptible.

Do not use Sirturo (bedaquiline) for the treatment of drug-sensitive (DS) tuberculosis; latent infection due to *Mycobacterium tuberculosis;* and extra-pulmonary tuberculosis infections caused by non-tuberculous mycobacteria. The safety and efficacy of Sirturo (bedaquiline) in the treatment of HIV infected patients with MDR-TB have not been established as clinical data are limited.

The antibacterial activity of cycloserine results from inhibition of cell-wall synthesis in susceptible strains of gram-positive and gram-negative bacteria.

Pretomanid is an oral nitroimidazooxazine antimycobacterial drug. Pretomanid kills actively replicating *M. tuberculosis* by inhibiting mycolic acid biosynthesis, thereby blocking cell wall production. Under anaerobic conditions, against non-replicating bacteria, pretomanid acts as a respiratory poison following nitric oxide release. All of these activities require nitro-reduction of pretomanid within the mycobacterial cell by the deazaflavin-dependent nitroreductase (Ddn), which is dependent on the reduced form of the cofactor F_{420}. Reduction of F_{420} is accomplished by the F_{420} -dependent glucose-6-phosphate dehydrogenase, Fgd1.

Sirturo (bedaquiline) is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in *M. tuberculosis*.

Definitions:

Maricopa County contact for TB Control and Prevention:
https://www.maricopa.gov/2269/TB-Control-Prevention

Centers for Disease Ccontrol (CDC) multi-drug-resistant tuberculosis (MDR TB):
- Resistant to at least isoniazid and rifampin

Centers for Disease Control (CDC) extensive drug-resistant tuberculosis (XDR TB):
- A rare type of MDR TB that is resistant to isoniazid **and** rifampin **plus** any fluoroquinolone **and** at least **one of three** injectable second-line drugs such as amikacin, kanamycin, or capreomycin.

CYCLOSERINE
PRETOMANID
SIRTURO® (bedaquiline)

Directly observed treatment, short-course (DOTS): also known as (TB-DOTS)

- A tuberculosis (TB) control strategy recommended by the World Health Organization (WHO)
- The patient takes the medical regimen while a health care worker watches
- DOTS has five main components:
    - Government commitment (including political will at all levels, and establishment of a centralized and prioritized system of TB monitoring, recording and training)
    - Case detection by sputum smear microscopy
    - Standardized treatment regimen directly of six to nine months observed by a healthcare worker or community health worker for at least the first two months
    - Drug supply
    - A standardized recording and reporting system that allows assessment of treatment results

WHO consolidated guidelines on drug-resistant TB treatment:

Drugs reclassified into three groups (A, B and C) for the purpose of composing longer regimen:

- Group A includes three drugs to be prioritized and used, if possible, in all regimens:
    - levofloxacin/moxifloxacin, BDQ and LZD
- Group B includes two drugs to be possibly added to all regimens
    - Clofazimine and cycloserine/terizidone
- Group C includes "other" agents (including injectables) to be used as a substitute to complete a regimen of at least **four** drugs when agents from groups A and B cannot be used

Duration:

- Longer regimen: may be standardized or individualized; duration 18–20 months, modified depending upon patient response
- Shorter regimen: 9–12 months

Second-line drugs for drug resistant tuberculosis		
Group A	Group B	Group C
Levofloxacin or Moxifloxacin	Clofazimine	Ethambutol
Sirturo (bedaquiline)	Cycloserine or Terizidone	Delamanid
Linezolid		Pyrazinamide
		Imipenem-cilastatin or Meropenem
		Amikacin or Streptomycin
		Ethionamide or Prothionmide
		p-aminosalicylic acid (PAS)

CYCLOSERINE
PRETOMANID
SIRTURO® (bedaquiline)

Clinical strategy to build an individualized treatment regimen for MDR-TB	
• Build a regimen **using five or more drugs to which the isolate is susceptible (or has low likelihood of resistance)**, preferably with drugs that have not been used to treat the patient previously. • Choice of drugs is contingent on capacity to appropriately monitor for significant adverse effects, patient comorbidities, and preferences/values (choices therefore subject to program and patient safety limitations). • In children with TB disease who are contacts of infectious MDR-TB source cases, the source case's isolate drug susceptibility testing (DST) result should be used if an isolate is not obtained from the child. • **TB expert medical consultation is recommended (ungraded good practice statement).**	
Step 1: Choose ***one*** later-generation fluoroquinolone	Levofloxacin
	Moxifloxacin
Step 2: Choose ***both*** of these prioritized drugs	Sirturo (bedaquiline)
	Linezolid
Step 3: Choose ***both*** of these prioritized drugs	Clofazimine
	Cycloserine or Terizidone
Step 4: If a regimen cannot be assembled with five effective oral drugs, **and the isolate is susceptible**, use ***one*** of these injectable agents	Amikacin
	Streptomycin
Step 5: If needed or if oral agents preferred over injectable agents in Step 4, use the following drugs	Delamanid
	Pyrazinamide
	Ethambutol
Step 6: If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs	Ethionamide or Prothionmide
	Imipenem-cilastatin or Meropenem
	p-aminosalicylic acid (PAS)
	High-dose Isoniazid
The following are *no longer recommended* for inclusion in MDR-TB regimens	Capreomycin and kanamycin
	Amoxicillin clavulanate (when used without a carbapenem
	Aztreomycin and clarithromycin
Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis: an official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med 2019; 200:e93	

Resources:

Seromycin (cycloserine) product information, revised by Parsolex Gmp Center, Inc. 12-2019, at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2021.

Pretomanid product information, revised by Mylan Specialty, L.P. 04-2020, at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2021.

Sirtura (bedaquiline) product information, revised by Janssen Products, LP. 05-2020, at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2021.

CYCLOSERINE
PRETOMANID
SIRTURO® (bedaquiline)

Drew RH, Sterling TR. Antituberculosis drugs: An overview. In: UpToDate, Bernardo J, Baron EL (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on February 19, 2021.

Sterling TR. Treatment of drug-susceptible pulmonary tuberculosis in HIV-uninfected adults. In: UpToDate, Bernardo J, Baron EL (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on February 19, 2021.

Schluger NW, Heysell SK, Friedland G. Treatment of drug-resistant pulmonary tuberculosis in adults. In: UpToDate, Bernardo J, Baron EL (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on February 19, 2021.

WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO. At https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/ Accessed February 12, 2020. Re-reviewed on March 01, 2021.

WHO guidelines on tuberculosis infection prevention and control, 2019 update, Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO. At https://www.who.int/tb/publications/2019/guidelines-tuberculosis-infection-prevention-2019/en/ Accessed February 12, 2020. Re-reviewed on March 01, 2021.

Pontali E, Raviglione MC, Migliori GB, et al.: Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. Eur Respir Rev 2019; 28: 190035 [https://doi.org/10.1183/16000617.0035-2019]. Accessed February 12, 2020. Re-reviewed on March 01, 2021.