BlueCross BlueShield of Arizona
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**PHARMACY COVERAGE GUIDELINES**
**SECTION: DRUGS**

**ORIGINAL EFFECTIVE DATE: 2/13/2020**
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# PRETOMANID oral tablet
# SIRTURO® (bedaquiline) oral 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)

## PRETOMANID oral tablet
## SIRTURO® (bedaquiline) oral tablet

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

# Pretomanid

**Criteria:**

- **Criteria for initial 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:
   - Extensive drug resistant (XDR TB)
   - Treatment-intolerant multi-drug resistant (TI-MDR TB)
   - Nonresponsive multi-drug resistant (NR-MDR TB)

4. Individual is diagnosed by and will be followed by a Tuberculosis Clinic for directly observed therapy (DOT) with a combination regimen of Pretomanid, Sirturo (bedaquiline), and linezolid (brand Zyvox or generic)

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

6. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - Alanine aminotransferase
   - Aspartate aminotransferase
   - Alkaline phosphatase
   - Bilirubin
   - Serum potassium, calcium, and magnesium, if abnormal has been corrected
   - Electrocardiogram (ECG)

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

## PRETOMANID oral tablet
## SIRTURO® (bedaquiline) oral tablet

**Initial approval duration**: 26 weeks

- **Criteria for continuation of coverage (renewal request):** Pretomanid is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Infectious Disease Specialist

2. Individual is followed by a Tuberculosis Clinic for directly observed therapy (DOT) with a combination regimen of Pretomanid, Sirturo (bedaquiline), and linezolid (brand Zyvox or generic)

3. Individual's condition responded while on therapy
    - Response is defined as:
        - No evidence of disease progression
        - Functionality retained in most activities of daily living
        - Documented evidence of efficacy, disease stability and/or improvement

4. The indication for use is one that requires a longer duration than the usual 26 weeks for pulmonary tuberculosis the is either XDR-TB, TI-MDR TB, or NR-MDR TB

5. Individual has been adherent with the medication

6. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Significant adverse effect such as:
        - Clinically significant ventricular arrhythmia from Sirturo (bedaquilin)
        - A QTcF interval of > 500 ms from Sirturo (bedaquilin) confirmed by repeat ECG
        - QT prolongation from Sirturo (bedaquilin)
        - Hepatic toxicity from linezolid (brand Zyvox or generic) or Sirturo (bedaquiline)
        - Myelosuppression (including anemia, leukopenia, thrombocytopenia, and pancytopenia) from linezolid (brand Zyvox or generic)
        - Peripheral neuropathy from linezolid (brand Zyvox or generic)
        - Optic neuropathy from linezolid (brand Zyvox or generic)
        - Lactic acidosis from linezolid (brand Zyvox or generic)

7. There are no significant interacting drugs

**Renewal duration**: 10 weeks

## PRETOMANID oral tablet
## SIRTURO® (bedaquiline) oral tablet

## Sirturo (bedaquiline)

**Criteria:**

- **Criteria for initial 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 12 years of age and weighs at least 30 kg or older

  3. A confirmed diagnosis pulmonary multi-drug resistant (MDR) tuberculosis (TB)

  4. Individual is diagnosed by and will be followed by a Tuberculosis Clinic for directly observed therapy (DOT) 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

  5. Individual does not have **ANY** of the following conditions:
     - Drug-sensitive (DS) tuberculosis;
     - Latent infection due to *Mycobacterium tuberculosis;*
     - Extra-pulmonary tuberculosis infections caused by non-tuberculous mycobacteria
     - HIV infected individual with MDR TB

  6. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Electrocardiogram (ECG)
     - Assessment for signs and symptoms of liver disease
     - Serum potassium, calcium, and magnesium and correct if abnormal
     - Alanine aminotransferase
     - Aspartate aminotransferase
     - Alkaline phosphatase
     - Bilirubin

  **Initial approval duration**: 24 weeks

- **Criteria for continuation of coverage (renewal request):** Sirturo (bedaquiline) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Infectious Disease Specialist

## PRETOMANID oral tablet
## SIRTURO® (bedaquiline) oral tablet

2. Individual is followed by a Tuberculosis Clinic for directly observed therapy (DOT) 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

3. Individual's condition responded while on therapy
    - Response is defined as:
        - No evidence of disease progression
        - Functionality retained in most activities of daily living
        - Documented evidence of efficacy, disease stability and/or improvement

4. The indication for use is one that requires a longer duration than the usual 24 weeks for pulmonary multi-drug resistant (MDR) tuberculosis (TB)

5. Individual has been adherent with the medication

6. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Clinically significant ventricular arrhythmia from Sirturo (bedaquilin)
        - A QTcF interval of > 500 ms from Sirturo (bedaquilin) confirmed by repeat ECG
        - QT prolongation from Sirturo (bedaquilin)
        - Hepatic toxicity from linezolid (brand Zyvox or generic) or Sirturo (bedaquiline)
        - Myelosuppression (including anemia, leukopenia, thrombocytopenia, and pancytopenia) from linezolid (brand Zyvox or generic)
        - Peripheral neuropathy from linezolid (brand Zyvox or generic)
        - Optic neuropathy from linezolid (brand Zyvox or generic)
        - Lactic acidosis from linezolid (brand Zyvox or generic)

7. There are no significant interacting drugs

**Renewal duration**: 10 weeks

**Description:**

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).

## PRETOMANID oral tablet
## SIRTURO® (bedaquiline) oral tablet

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.

Sirturo (bedaquiline) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adult and pediatric patients (12 to less than 18 years of age and weighing at least 30 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.

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:**

**Centers for Disease Ccontrol (CDC) multi-drug-resistant tuberculosis (MDR TB):**

- Resistant to at least isoniazid and rifampin

## PRETOMANID oral tablet
## SIRTURO® (bedaquiline) oral tablet

**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.

**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

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

**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
    - CFZ 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) |

## PRETOMANID oral tablet
## SIRTURO® (bedaquiline) oral tablet

**Resources:**

Pretomanid product information accessed 01-31-20 at DailyMed

Sirtura (bedaquiline) product information accessed 01-31-20 at DailyMed

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]

WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO

WHO guidelines on tuberculosis infection prevention and control, 2019 update, Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO.