

## PHARMACY COVERAGE GUIDELINE

### Cycloserine Pretomanid SIRTURO® (bedaquiline) Generic Equivalent (if available)

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#### **This Pharmacy Coverage Guideline (PCG):**

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively “Service”) is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider’s judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member’s benefit plan; and
- Is subject to change as new information becomes available.

#### **Scope**

- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

#### **Instructions & Guidance**

- To determine whether a member is eligible for the Service, read the entire PCG.
  - This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
  - Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
  - The “[Criteria](#)” section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member’s benefit plan.
  - The “[Description](#)” section describes the Service.
  - The “[Definition](#)” section defines certain words, terms or items within the policy and may include tables and charts.
  - The “[Resources](#)” section lists the information and materials we considered in developing this PCG
  - **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
  - Information about medications that require prior authorization is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy). You must fully complete the [request form](#) and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to [Pharmacyprecert@azblue.com](mailto:Pharmacyprecert@azblue.com).
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## Medical Necessity Requirements for Cycloserine

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### Criteria for Initial Therapy:

#### **Prescriber Qualifications**

- Prescribed by a Pulmonologist or Infectious Disease Specialist, or in consultation with one

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#### Indication

- Active pulmonary or extra-pulmonary tuberculosis (including renal disease) where the causative organism must be susceptible to cycloserine and when the treatment with primary tuberculosis (TB) medications are proven to be inadequate

#### Age Requirement

- 18 years or older

#### Baseline Clinical Evaluation

- Culture and sensitivity report shows susceptibility to cycloserine
- Susceptibility to other anti-tuberculosis agents in regimen
- Supervised by and undertaken by the appropriate state or local agency Tuberculosis Clinic responsible for a video directly observed therapy (vDOT)
- Must be used within a combination regimen of other drugs with known susceptibility for tuberculosis

#### Alternative Therapies

- Failure contraindication, intolerance to **ALL** the following:
  - Streptomycin
  - Isoniazid
  - Rifampin
  - Ethambutol

#### Safety

- No FDA-label contraindications such as:
  - Epilepsy
  - Severe renal insufficiency
  - Excessive alcohol use
  - Depression
  - Severe anxiety
  - Psychosis

#### Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (culture and sensitivity, susceptibility testing)
  - Supporting clinical documentation

#### Initial Therapy Criteria Approval Duration:

- 6 months OR end of plan year

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#### Criteria for Continuation of Therapy (renewal therapy)

**Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy**

##### Prescriber Qualification

- Continues to be seen by a Pulmonologist or Infectious Disease Specialist, or in consultation

##### Clinical Response

- Documented evidence of efficacy, disease stability and/or improvement
- No evidence of disease progression or unacceptable toxicity

##### Adherence

- Adherence to the prescribed therapy regimen has been documented

##### Safety

- No new contraindications or significant adverse drug effects such as:
  - Convulsions
  - Serious psychosis or depression
  - Suicidal behaviors or tendencies
  - Severe anxiety
  - Allergic dermatitis
  - Epilepsy
  - Severe renal insufficiency
  - Excessive alcohol use

##### Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use

##### Continuation Therapy Criteria Approval Duration:

- 12 months OR end of plan year
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## Medical Necessity Requirements for Pretomanid

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#### Criteria for Initial Therapy:

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#### Prescriber Qualifications

- Prescribed by an Infectious Disease Specialist or Pulmonologist, or in consultation with an Infectious Disease Specialist or Pulmonologist

#### Indication

- Pulmonary tuberculosis that is **ONE** of the following:
  - Resistant to isoniazid, rifamycins, fluoroquinolone and second line injectable antibacterial drug
  - Resistant to isoniazid and rifampin, who are treatment-intolerant or nonresponsive to standard therapy

#### Age Requirement

- 18 years or older

#### Baseline Clinical Evaluation

- Susceptibility information for background regimen against *Mycobacterium tuberculosis* isolate
- Alanine aminotransferase
- Alkaline phosphatase
- Aspartate aminotransferase
- Bilirubin
- Serum potassium, calcium, and magnesium (must be corrected if abnormal)
- Electrocardiogram
- Complete blood count
- Supervised by and undertaken by the appropriate state or local agency Tuberculosis Clinic responsible for a video directly observed therapy (vDOT)
- Must be used within a combination regimen of Sirturo (bedaquiline) and linezolid (brand Zyvox or generic)
- Duration of therapy must be submitted with request

#### Safety

- Does not have **ANY** of the following:
  - Concomitant drug use with moderate or strong CYP3A4 inducers (e.g., dexamethasone, nafcillin, phenobarbital, carbamazepine, phenytoin, others)
  - Drug-sensitive tuberculosis
  - Latent infection due to *Mycobacterium tuberculosis*
  - Extra-pulmonary infection due to *Mycobacterium tuberculosis*
  - Infections caused by non-tuberculous mycobacteria
  - TB resistant to isoniazid and rifampin, who are responsive to standard therapy and not treatment intolerant
  - TB with known resistance to any component of the combination
  - FDA-labeled contraindications to the use of Sirturo (bedaquiline) or linezolid

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- Hepatic impairment
- Renal impairment

#### Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (susceptibility testing, liver enzymes, electrolytes, ECG, CBC)
  - Supporting clinical documentation

#### Initial Therapy Criteria Approval Duration:

- 26 weeks OR end of plan year
    - Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 26 weeks, if necessary
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### Criteria for Continuation of Therapy (renewal therapy)

**Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy**

#### Prescriber Qualification

- Continues to be seen by an Infectious Disease Specialist or Pulmonologist, or in consultation

#### Clinical Response

- Documented evidence of efficacy, disease stability and/or improvement
- No evidence of disease progression or unacceptable toxicity
- Indication requires longer duration than usual 26 weeks for pulmonary tuberculosis (documentation of duration is required)

#### Adherence

- Adherence to the prescribed therapy regimen has been documented

#### Safety

- Does not have **ANY** of the following:
  - No concomitant drug use with moderate or strong CYP3A4 inducers (e.g., dexamethasone, nafcillin, phenobarbital, carbamazepine, phenytoin, others)
  - QT prolongation from Sirturo
  - Clinically significant ventricular arrhythmia from Sirturo
  - Hepatotoxicity from linezolid or Sirturo
  - Myelosuppression from linezolid
  - Peripheral neuropathy from linezolid
  - Optic neuropathy from linezolid

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- Lactic acidosis from linezolid
- Drug-sensitive tuberculosis
- Latent infection due to *Mycobacterium tuberculosis*
- Extra-pulmonary infection due to *Mycobacterium tuberculosis*
- Infections caused by non-tuberculous mycobacteria
- TB resistant to isoniazid and rifampin, who are responsive to standard therapy and not treatment intolerant
- TB with known resistance to any component of the combination
- FDA-labeled contraindications to the use of Sirturo (bedaquiline) or linezolid
- Hepatic impairment
- Renal impairment

#### Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in pulmonary tuberculosis
- Lab values confirming safe use (electrolytes, ECG, liver enzymes, CBC)

#### Continuation Therapy Criteria Approval Duration:

- 13 weeks OR end of plan year
  - Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 26 weeks to a total of 39 weeks, if necessary

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## Medical Necessity Requirements for SIRTURO (bedaquiline)

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### Criteria for Initial Therapy:

#### Prescriber Qualifications

- Prescribed by an Infectious Disease Specialist or Pulmonologist, or in consultation with an Infectious Disease Specialist or Pulmonologist

#### Indication

- Pulmonary tuberculosis due to *Mycobacterium tuberculosis* resistant to at least rifampin and isoniazid

#### Age Requirement

- 5 years or older and weight is at least 15 kilograms

#### Baseline Clinical Evaluation

- Susceptibility information for background regimen against *Mycobacterium tuberculosis* isolate

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- Alanine aminotransferase
- Alkaline phosphatase
- Aspartate aminotransferase
- Bilirubin
- Serum potassium, calcium, and magnesium (must be corrected if abnormal)
- Electrocardiogram
- Supervised by and undertaken by the appropriate state or local agency Tuberculosis Clinic responsible for a video directly observed therapy (vDOT)
- Must be used within a combination regimen with at least 3 other drugs to which tuberculosis is shown to be susceptible or with at least 4 other drugs to which tuberculosis is likely to be susceptible

#### Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. Note: Any failure, contraindication, or intolerance to the generic drugs should be reported to the Food and Drug Administration (see Definitions section)

#### Contraindications and Drug-Drug Interactions

- Does not have **ANY** of the following:
  - No concomitant drug use with moderate or strong CYP3A4 inducers (e.g., dexamethasone, nafcillin, phenobarbital, carbamazepine, phenytoin, rifampin, rifapentine, rifabutin, others)
  - Drug-sensitive tuberculosis
  - Latent infection due to *Mycobacterium tuberculosis*
  - Extra-pulmonary tuberculosis
  - Infections caused by non-tuberculous mycobacteria
  - TB resistant to isoniazid and rifampin, who are responsive to standard therapy and not treatment intolerant
  - TB with known resistance to any component of the combination
  - Contraindications to the use of Pretomanid and linezolid
  - Ventricular arrhythmias, risk factors for QT prolongation (e.g., torsades de pointes, congenital long QT syndrome), or a recent myocardial infarction

#### Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (susceptibility testing, liver enzymes, electrolytes, ECG)
  - Supporting clinical documentation

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#### Initial Therapy Criteria Approval Duration:

- 24 weeks OR end of plan year
  - Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 24 weeks to a total of 39 weeks, if necessary

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#### Criteria for Continuation of Therapy (renewal therapy)

**Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy**

#### Prescriber Qualification

- Continues to be seen by an Infectious Disease Specialist or Pulmonologist, or in consultation

#### Clinical Response

- Documented evidence of efficacy, disease stability and/or improvement
- No evidence of disease progression or unacceptable toxicity
- Indication requires longer duration than usual 24 weeks for pulmonary tuberculosis (documentation of duration is required)

#### Adherence

- Adherence to the prescribed therapy regimen has been documented

#### Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. Note: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

#### Safety

- Does not have **ANY** of the following:
  - No concomitant drug use with moderate or strong CYP3A4 inducers (e.g., dexamethasone, nafcillin, phenobarbital, carbamazepine, phenytoin, rifampin, rifapentine, rifabutin, others)
  - QT prolongation greater than 500 milliseconds (confirmed with repeat electrocardiogram) from Sirturo
  - Clinically significant ventricular arrhythmia from Sirturo
  - Hepatotoxicity from linezolid or Sirturo
  - Myelosuppression from linezolid
  - Peripheral neuropathy from linezolid
  - Optic neuropathy from linezolid
  - Lactic acidosis from linezolid
  - Drug-sensitive tuberculosis
  - Latent infection due to *Mycobacterium tuberculosis*
  - Extra-pulmonary tuberculosis

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- Infections caused by non-tuberculous mycobacteria
- TB resistant to isoniazid and rifampin, who are responsive to standard therapy and not treatment intolerant
- TB with known resistance to any component of the combination
- Contraindications to the use of Pretomanid and linezolid

#### Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in pulmonary tuberculosis
- Lab values confirming safe use (electrolytes, ECG, liver enzymes)

#### Continuation Therapy Criteria Approval Duration:

- 15 weeks OR end of plan year
  - Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 24 weeks to a total of 39 weeks, if necessary

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#### Criteria for Off-Label Use Requests:

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 Non-Cancer Medications
2. Off-Label Use of Cancer Medications

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#### 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 an antimycobacterial agent indicated, as part of a combination regimen with Sirturo (bedaquiline) and linezolid (brand Zyvox or generic) for the treatment of adults with pulmonary tuberculosis (TB) that is resistant to isoniazid, rifamycins, a fluoroquinolone and a second line injectable antibacterial drug OR adults with pulmonary TB resistant to isoniazid and rifampin, who are treatment-intolerant or nonresponsive to standard

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therapy. The approval of this indication is based on limited clinical safety and efficacy data and is indicated for use in a limited and specific population of patients.

The safety and effectiveness of Pretomanid have not been established for use in combination with drugs other than Sirturo (bedaquiline) and linezolid (brand Zyvox or generic). 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 is **not indicated** in individuals 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 individuals (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 individual'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 individuals with MDR-TB have not been established as clinical data are limited.

Options for empiric treatment for drug-resistant TB include an expanded regimen (six or more drugs) or an abbreviated regimen of bedaquiline, pretomanid, and linezolid (BPaL) or BPaL plus moxifloxacin (BPaLM). BPaL or BPaLM may be a useful alternative regimen for individuals who are failing or intolerant of an expanded empiric regimen.

An expanded empiric regimen usually consists of first-line drugs (isoniazid, rifampin, and pyrazinamide) plus two or more additional drugs. Severe systemic infection (such as meningitis or miliary disease) should stimulate the addition of at least three additional second-line drugs. This might include use of a fluoroquinolone (levofloxacin or moxifloxacin), bedaquiline, and/or another core second-line agent.

The use of a longer, individualized regimen consists of an intensive phase (with administration of at least 5 effective drugs) for at least 5-7 months after sputum culture conversion, followed by a continuation phase (with administration of at least 4 effective drugs) for 15-24 months beyond sputum culture conversion.

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Use of a longer, individualized regimen includes disseminated, meningeal, central nervous system disease, or bone involvement; advanced HIV infection (CD4<50 cells/microL) and extrapulmonary disease; pregnancy; extensive (or advanced) TB disease, such as bilateral cavitory disease or extensive parenchymal damage on chest radiography; and contraindication to one or more drugs in the shorter course regimens.

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<sub>420</sub>. Reduction of F<sub>420</sub> is accomplished by the F<sub>420</sub>-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*.

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#### **Definitions:**

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting  
[MedWatch Forms for FDA Safety Reporting | FDA](#)

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

#### **Drug-resistant tuberculosis (DR-TB):**

- Isolate with resistance to one or more antituberculosis drugs

#### **Monoresistant tuberculosis:**

- Isolate with resistance to a single antituberculosis drug

#### **Polyresistant tuberculosis:**

- Isolate resistant to more than one antituberculosis drug; may be resistant to either isoniazid or rifampin but not to both

#### **Multi-drug-resistant tuberculosis (MDR TB):**

- Resistant to at least isoniazid and rifampin and possibly additional antituberculosis agents

#### **Pre-extensive drug-resistant tuberculosis (pre-XDR TB):**

- Resistance to isoniazid and rifampin as well as a fluoroquinolone (levofloxacin or moxifloxacin) OR resistance to isoniazid, rifampin, and at least one second-line injectable agent (amikacin, capreomycin, kanamycin)

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#### **Rifampicin-resistant TB (RR-TB):**

- TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line or second-line TB medicines

#### **Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB):**

- TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin

#### **Extensive drug-resistant tuberculosis (XDR TB):**

- A type of MDR TB that is resistant to isoniazid, rifampin, a fluoroquinolone (levofloxacin or moxifloxacin) and at least one second-line injectable drug (such as amikacin, capreomycin, kanamycin) OR resistance to isoniazid, rifampin, a fluoroquinolone, and either bedaquiline or linezolid

#### **Primary drug resistance:**

- Drug resistance in an individual who has never received antituberculosis therapy

#### **Secondary drug resistance:**

- Development of resistance during or following antituberculosis therapy in individuals who had previously had drug-susceptible tuberculosis

#### **Tuberculosis infection (newer term):**

- Clinical state in which there is evidence of specific cell-mediated immunologic response following exposure to *Mycobacterium tuberculosis*-derived protein antigens in solution (e.g., positive tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA), in the absence of signs or symptoms of illness
- Older term:
  - Latent tuberculosis infection

#### **Tuberculosis disease (newer term):**

- Presence of signs or symptoms reflecting illness due to *M. tuberculosis* complex
- *M. tuberculosis* complex includes 8 distinct but closely related organisms – *M. bovis*, *M. caprae*, *M. africanum*, *M. microti*, *M. pinnipedii*, *M. mungi*, *M. orygis* and *M. canetti*
- Older terms:
  - Active tuberculosis
  - Active tuberculosis disease
  - Active tuberculosis infection

#### **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 observes the patient
- 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

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- 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

#### **First-line drugs for treatment of drug-susceptible tuberculosis:**

- Isoniazid
- Rifampin (rifampicin)
- Rifabutin
- Rifapentine
- Pyrazinamide
- Ethambutol

#### **Second-line antituberculosis drugs:**

- Amikacin
- Amoxicillin-clavulanate (co-administered with imipenem-cilastatin or meropenem)
- Bedaquiline
- Capreomycin
- Clofazimine (not commercially available in the United States)
- Cycloserine
- Delamanid
- Ethambutol
- Ethionamide
- Imipenem-cilastatin
- Isoniazid, high dose
- Kanamycin
- Levofloxacin
- Linezolid
- Meropenem
- Moxifloxacin
- Para-aminosalicylic acid
- Pretomanid
- Pyrazinamide
- Streptomycin
- Thioacetazone (not available in the United States)

#### **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

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- 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

Medications for use in longer multi-drug resistant tuberculosis		
Group A – include all 3	Group B – add one or both	Group C – add to complete the regimen and when medications from Groups A and B cannot be used
Levofloxacin or Moxifloxacin	Clofazimine	Ethambutol
Sirturo (bedaquiline)	Cycloserine or Terizidone	Delamanid
Linezolid		Pyrazinamide
		Imipenem-cilastatin or Meropenem
		Amikacin or Streptomycin
		Ethionamide or Prothionide
		p-aminosalicylic acid (PAS)

Clinical strategy to build an individualized treatment regimen for MDR-TB	
<p>If a standardized short course regimen (such as BPaL: bedaquiline, pretomanid, and linezolid) cannot be used due to drug resistance, drug intolerance or limited drug availability, an individualized regimen may be created according to the following principles.</p> <ul style="list-style-type: none"> <li>Build a regimen <b>using five or more drugs to which the isolate is susceptible (or has low likelihood of resistance)</b>, preferably with drugs that have not been used to treat the patient previously.</li> <li>Choice of drugs is contingent on capacity to appropriately monitor for significant adverse effects, patient comorbidities, and preferences/values (choices therefore are subject to program and patient safety limitations).</li> <li>In children with TB disease who are contacts of MDR-TB source cases, if an isolate cannot be obtained from the child, the source case's isolate drug susceptibility testing (DST) result should be used.</li> <li><b>TB expert medical consultation is recommended.</b></li> </ul>	
<b>Step 1:</b> Choose <b>one</b> later-generation fluoroquinolone	Levofloxacin Moxifloxacin
<b>Step 2:</b> Choose <b>both</b> of these prioritized drugs	Sirturo (bedaquiline) Linezolid
<b>Step 3:</b> Choose <b>one or both</b> of these prioritized drugs	Clofazimine Cycloserine or Terizidone
<b>Step 4:</b> If needed, use the following drugs	Pyrazinamide Delamanid Ethambutol Ethionamide or Prothionide
<p>Patient preferences in terms of the harms and benefits associated with injectables (the use of which is no longer obligatory), the capacity to appropriately monitor for</p>	

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## PHARMACY COVERAGE GUIDELINE

### Cycloserine Pretomanid SIRTURO® (bedaquiline) Generic Equivalent (if available)

significant adverse effects, consideration of drug–drug interactions, and patient comorbidities should be considered in selecting Step 4 agents over injectables.	Imipenem-cilastatin or Meropenem Plus Amoxicillin clavulanate (to obtain use of clavulanate)
	p-aminosalicylic acid (PAS)
	High-dose Isoniazid
<b>Step 5:</b> If a regimen cannot be assembled with five effective oral drugs, <b>and the isolate is susceptible</b> , use <b>one</b> of these injectable agents	Amikacin
	Streptomycin
<b>The following are <u>no longer recommended</u> for inclusion in MDR-TB regimens</b>	Capreomycin and kanamycin
	Amoxicillin clavulanate (when used without a carbapenem)
	Azithromycin and clarithromycin
<i>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</i>	

#### **The following may increase the risk for QT prolongation when patients are receiving SIRTURO:**

- use with other QT prolonging drugs including fluoroquinolones and macrolide
- antibacterial drugs and the antimycobacterial drug, clofazimine
- a history of Torsade de Pointes
- a history of congenital long QT syndrome
- a history of or ongoing hypothyroidism
- a history of or ongoing bradyarrhythmias
- a history of uncompensated heart failure
- serum calcium, magnesium, or potassium levels below the lower limits of normal

#### **Resources:**

Cycloserine product information, revised by Dr. Reddy's Laboratories, Inc. 02-2023. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed February 18, 2025.

Pretomanid product information, revised by Viatris Specialty, LLC. 11-2024. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed February 18, 2025.

Sirturo (bedaquiline) product information, revised by Janssen Products, LP. 06-2024. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed February 18, 2025.

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. Available at <http://uptodate.com>. Literature current through January 2025. Topic last updated January 30, 2025. Accessed February 22, 2025.

WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. License: CC BY-NC-SA 3.0 IGO. Accessed February 22, 2025.