BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

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

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 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. 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.

Criteria:

Cycloserine

➢ **Criteria for Initial therapy:** Cycloserine is considered ***medically necessary*** and will be approved when **ALL** 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. Individual has a confirmed diagnosis of active pulmonary or extra-pulmonary tuberculosis (including renal disease) where the causative organism is susceptible to cycloserine and when treatment with primary tuberculosis (TB) medications are proven to be inadequate

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

5. Must be used within a combination regimen of other drugs with known susceptibility for tuberculosis

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

7. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ALL** the following:
    a. Streptomycin
    b. Isoniazid
    c. Rifampin
    d. Ethambutol

8. There are **NO** FDA-label contraindications such as:
    a. Epilepsy
    b. Severe renal insufficiency
    c. Excessive concurrent use of alcohol
    d. Depression
    e. Severe anxiety
    f. Psychosis

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cycloserine is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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

2. Individual's condition has responded while on therapy with response defined as the following:
    a. Documented evidence of efficacy, disease stability and/or improvement
    b. There is no evidence of disease progression or unacceptable toxicity

3. The indication for use is one that requires a longer duration than the usual duration

4. Individual has been adherent with the medication

5. Individual has not developed any contraindications or significant adverse drug effects that may exclude continued use such as:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Convulsions
        ii. Significant/serious psychosis or depression
        iii. Suicidal behaviors or tendencies
        iv. Allergic dermatitis

Renewal duration: 12 months

- 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**

Pretomanid

- **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 or Pulmonologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of pulmonary tuberculosis (TB) that is **ONE** of the following:
    a. Resistant to isoniazid, rifamycins, fluoroquinolone and second line injectable antibacterial drug
    b. Resistant to isoniazid and rifampin, who are treatment-intolerant or nonresponsive to standard therapy

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

5. Must be used within a combination regimen of Sirturo (bedaquiline), and linezolid (brand Zyvox or generic)

6. Individual does not have **ANY** of the following conditions:
    a. Drug-sensitive tuberculosis (DSTB)

b. Latent infection due to *Mycobacterium tuberculosis*
c. Extra-pulmonary infection due to *Mycobacterium tuberculosis*
d. Infections caused by non-tuberculous mycobacteria
e. TB resistant to isoniazid and rifampin, who are responsive to standard therapy and not treatment intolerant
f. TB with known resistance to any component of the combination
g. FDA-label contraindications to the use of Sirturo (bedaquiline) or linezolid
h. Hepatic impairment
i. Renal impairment

7. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Susceptibility information for background regimen against *M. tuberculosis* isolate
   b. Alanine aminotransferase
   c. Alkaline phosphatase
   d. Aspartate aminotransferase
   e. Bilirubin
   f. Serum potassium, calcium, and magnesium, must be corrected if abnormal
   g. Electrocardiogram (ECG)
   h. Complete blood count

8. Duration of therapy must be submitted with request

9. Individual is not currently taking any drugs which can result in a significant drug interaction requiring discontinuation such as use with moderate or strong CYP3A4 inducers (e.g., dexamethasone, nafcillin, phenobarbital, carbamazepine, phenytoin, others)

Initial Approval duration: 26 weeks
Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 26 weeks, if necessary

- **Criteria for continuation of coverage (renewal request):** Pretomanid is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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

2. Individual's condition has responded while on therapy with response defined as the following:
   a. Documented evidence of efficacy, disease stability and/or improvement
   b. There is no evidence of disease progression or unacceptable toxicity

3. The indication for use is one that requires a longer duration than the usual 26 weeks for pulmonary tuberculosis (documentation of duration is required)

4. Individual has been adherent with the medication

5. Individual has not developed any contraindications or significant adverse drug effects that may exclude continued use such as: [when used as part of the combination regimen for TB]
    a. QT prolongation from Sirturo
    b. Clinically significant ventricular arrhythmia from Sirturo
    c. Hepatotoxicity (elevated transaminases and total bilirubin) from linezolid or Sirturo
    d. Myelosuppression (anemia, leukopenia, thrombocytopenia, and pancytopenia) from linezolid
    e. Peripheral neuropathy from linezolid
    f. Optic neuropathy from linezolid
    g. Lactic acidosis from linezolid

6. Individual is not currently taking any drugs which can result in a significant drug interaction requiring discontinuation such as use with moderate or strong CYP3A4 inducers (e.g., dexamethasone, nafcillin, phenobarbital, carbamazepine, phenytoin, others)

7. Individual does not have **ANY** of the following conditions:
    a. Drug-sensitive tuberculosis (DSTB)
    b. Latent infection due to Mycobacterium tuberculosis
    c. Extra-pulmonary infection due to Mycobacterium tuberculosis
    d. Infections caused by non-tuberculous mycobacteria
    e. TB resistant to isoniazid and rifampin, who are responsive to standard therapy and not treatment intolerant
    f. TB with known resistance to any component of the combination
    g. FDA-label contraindications to the use of Sirturo (bedaquiline) or linezolid
    h. Hepatic impairment
    i. Renal impairment

Renewal duration: 13 weeks
Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 26 weeks to a total of 39 weeks, if necessary

- 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**

SIRTURO (bedaquiline)

- **Criteria for Initial therapy:** Sirturo (bedaquiline) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Infectious Disease Specialist or Pulmonologist

2. Individual is 5 years of age or older and weighs at least 15 kg

3. Individual has a confirmed diagnosis of pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampin and isoniazid

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

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Must be used within a combination regimen with at least 3 other drugs to which the individual's TB is shown to be susceptible or with at least 4 other drugs to which the individual's TB is likely to be susceptible

7. Individual does not have **ANY** of the following conditions:
    a. Drug-sensitive tuberculosis (DSTB)
    b. Latent infection due to *Mycobacterium tuberculosis*
    c. Extra-pulmonary tuberculosis
    d. Infections caused by non-tuberculous mycobacteria
    e. TB resistant to isoniazid and rifampin, who are responsive to standard therapy and not treatment intolerant
    f. TB with known resistance to any component of the combination
    g. FDA-label contraindications to the use of Pretomanid and linezolid

8. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Susceptibility information for background regimen against *M. tuberculosis* isolate
    b. Alanine aminotransferase
    c. Alkaline phosphatase
    d. Aspartate aminotransferase
    e. Bilirubin
    f. Serum potassium, calcium, and magnesium and must be correct if abnormal
    g. Electrocardiogram (ECG)

9. Individual does not have ventricular arrhythmias, risk factors for QT prolongation (e.g., torsades de pointes, congenital long QT syndrome, others), or a recent myocardial infarction

10. Individual is not currently taking any drugs which can result in a significant drug interaction requiring discontinuation such as use with moderate or strong CYP3A4 inducers (e.g., dexamethasone, nafcillin,

phenobarbital, carbamazepine, phenytoin, rifampin, rifapentine, rifabutin, others)

Initial approval duration: 24 weeks
Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 24 weeks, if necessary

- **Criteria for continuation of coverage (renewal request):** Sirturo (bedaquiline) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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

2. Individual's condition has responded while on therapy with response defined as the following:
    a. Documented evidence of efficacy, disease stability and/or improvement
    b. There is no evidence of disease progression or unacceptable toxicity

3. The indication for use is one that requires a longer duration than the usual 24 weeks for pulmonary tuberculosis (documentation of duration is required)

4. Individual has been adherent with the medication

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has not developed any contraindications or significant adverse drug effects that may exclude continued use such as: [when used as part of the combination regimen for TB]
    a. QT prolongation of greater than 500ms (confirmed with repeat ECG) from Sirturo
    b. Clinically significant ventricular arrhythmia from Sirturo
    c. Hepatotoxicity (elevated transaminases and total bilirubin) from linezolid or Sirturo
    d. Myelosuppression (anemia, leukopenia, thrombocytopenia, and pancytopenia) from linezolid
    e. Peripheral neuropathy from linezolid
    f. Optic neuropathy from linezolid
    g. Lactic acidosis from linezolid

7. Individual does not have **ANY** of the following conditions:
    a. Drug-sensitive tuberculosis (DSTB)
    b. Latent infection due to *Mycobacterium tuberculosis*
    c. Extra-pulmonary tuberculosis
    d. Infections caused by non-tuberculous mycobacteria
    e. TB resistant to isoniazid and rifampin, who are responsive to standard therapy and not treatment intolerant
    f. TB with known resistance to any component of the combination

g. FDA-label contraindications to the use of Pretomanid and linezolid

8. Individual is not currently taking any drugs which can result in a significant drug interaction requiring discontinuation such as use with moderate or strong CYP3A4 inducers (e.g., dexamethasone, nafcillin, phenobarbital, carbamazepine, phenytoin, rifampin, rifapentine, rifabutin, others)

Renewal duration: 15 weeks
Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 24 weeks to a total of 39 weeks, if necessary

- 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**

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 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.

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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*.

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 cavitary 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_{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:

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)

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
    - 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
- 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

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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)

Clinical strategy to build an individualized treatment regimen for MDR-TB	
If a standardized short course regimen (such as BPaL: bedaquiline, pretonamid, 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. • 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 are subject to program and patient safety limitations). • In children with TB disease who are contacts of MDR-TB source cases, if an isolated cannot be obtained from the child, the source case's isolate drug susceptibility testing (DST) result should be used. • **TB expert medical consultation is recommended.**	
Step 1: Choose ***one*** later-generation fluoroquinolone	Levofloxacin
	Moxifloxacin
Step 2: Choose ***both*** of these prioritized drugs	Sirturo (bedaquiline)
	Linezolid
Step 3: Choose ***one or both*** of these prioritized drugs	Clofazimine
	Cycloserine or Terizidone
Step 4: If needed, use the following drugs 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 significant adverse effects, consideration of drug–drug interactions, and patient comorbidities should be considered in selecting Step 4 agents over injectables.	Pyrazinamide
	Delamanid
	Ethambutol
	Ethionamide or Prothionmide
	Imipenem-cilastatin or Meropenem Plus Amoxicillin clavulanate (to obtain use of clavulanate)
	p-aminosalicylic acid (PAS)
	High-dose Isoniazid
Step 5: If a regimen cannot be assembled with five effective oral drugs, **and the isolate is susceptible**, use ***one*** of these injectable agents	Amikacin
	Streptomycin
The following are *no longer recommended* for inclusion in MDR-TB regimens	Capreomycin and kanamycin
	Amoxicillin clavulanate (when used without a carbapenem)
	Azithromycin and clarithromycin

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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

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.