Clinical Policy: Bedaquiline (Sirturo)

Reference Number: PA.CP.PMN.212
Effective Date: 01/2020
Last Review Date: 01/2023

Revision Log

Description
Bedaquiline (Sirturo®) is a diarylquinoline antimycobacterial drug.

FDA Approved Indication(s)
Sirturo is indicated as part of combination therapy in the treatment of adult and pediatric patients (5 years and older and weighing at least 15 kg) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve Sirturo for use when an effective treatment regimen cannot otherwise be provided.*

Limitation(s) of use:
- Do not use Sirturo for the treatment of:
  - Latent infection due to *Mycobacterium tuberculosis*
  - Drug-sensitive tuberculosis
  - Extra-pulmonary tuberculosis
  - Infections caused by non-tuberculous mycobacteria
- The safety and efficacy of Sirturo in the treatment of HIV infected patients with MDR-TB have not been established as clinical data are limited.

**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*

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Sirturo is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Multi-Drug Resistant Tuberculosis without Pretomanid (must meet all)**:**

1. Diagnosis of MDR-TB;
2. Prescribed by or in consultation with an infectious disease specialist or a pulmonologist or expert in the treatment of tuberculosis (e.g., state or county public health department, specialists affiliated with TB Centers of Excellence as designated by the CDC, infectious disease specialists managing TB clinics);
3. Age ≥ 5 years;
4. Weight ≥ 15 kg;
5. Prescribed in combination with at least 3 other anti-tuberculosis agents (*Appendix B*);
6. Dose does not exceed one of the following (a or b):

a. Weight ≥ 30 kg: 400 mg per day for the first 2 weeks, followed by 200 mg three times per week;
b. Weight 15 to 29 kg: 200 mg per day for the first 2 weeks, followed by 100 mg three times per week.

Approval duration: 24 weeks

B. Multi-Drug Resistant Tuberculosis with Pretomanid (must meet all)**:**
1. Diagnosis of pulmonary MDR-TB or XDR-TB;
2. Prescribed by or in consultation with an expert in the treatment of tuberculosis (e.g., state or county public health department, specialists affiliated with TB Centers of Excellence as designated by the CDC, infectious disease specialists managing TB clinics);
3. Age ≥ 15 years;
4. Prescribed in combination with pretomanid and linezolid;
   **Prior authorization may be required for pretomanid and linezolid.*
5. One of the following (a or b):
   a. Prescribed in combination with moxifloxacin (off-label);
   b. Documented resistance to fluoroquinolones, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 400 mg per day for the first 2 weeks, followed by 200 mg three times per week.

Approval duration: 26 weeks

C. Other diagnoses/indications
1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Multi-Drug Resistant Tuberculosis without Pretomanid (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. Member has not received more than 24 weeks of Sirturo therapy;
4. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Weight ≥ 30 kg: 200 mg three times per week;
   b. Weight 15 to 29 kg: 100 mg three times per week.

Approval duration: up to a total duration of 24 weeks

B. Multi-Drug Resistant Tuberculosis with Pretomanid (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. Member meets one of the following (a or b):

a. Member continues to receive pretomanid and linezolid in combination with Sirturo;
b. Member continues to receive pretomanid and has completed at least 4 weeks of linezolid therapy;

4. If request is for treatment beyond 26 weeks, provider attestation of delayed treatment response within the first 8 weeks as assessed by time to culture conversion, persistent culture positivity, clinical response to treatment, and other underlying clinical factors, or modified based on adverse events;
5. If request is for a dose increase, new dose does not exceed 200 mg three times per week.

Approval duration: up to a total treatment duration of 26 weeks (9 months if evidence of delayed culture conversion)

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
CDC: Centers for Disease Control
FDA: Food and Drug Administration
MDR-TB: multi-drug resistant tuberculosis
XDR-TB: extensively drug resistant tuberculosis

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
amikacin/kanamycin	15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly	15 mg/kg/day
capreomycin	15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly	1,000 mg/day
cycloserine	10 to 15 mg/kg PO QD or BID	1,000 mg/day
ethambutol	Follow weight-based dosing in prescribing information	4,000 mg/dose

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ethionamide	10 to 20 mg/kg PO QD or BID	1,000 mg/day
imipenem-cilastatin*	1,000 mg IV BID	2,000 mg/day
levofloxacin	500 to 1,000 mg PO or IV QD	1,000 mg/day
linezolid	600 mg PO or IV QD	600 mg/day
meropenem*	2,000 mg IV BID or TID	6,000 mg/day
moxifloxacin	400 mg PO or IV QD	400 mg/day
para-aminosalicylic acid	8 to 12 g PO BID or TID	12 g/day
pyrazinamide	Follow weight-based dosing in prescribing information	4,000 mg/dose
streptomycin	15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly	20 mg/kg/day
pretomanid	200 mg PO QD for 26 weeks.	200 mg/day
linezolid	1,200 mg PO QD	1,200 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Amoxicillin-clavulanic acid should be coadministered with every dose of imipenem-cilastatin or meropenem but is not counted as a separate agent and should not be used as a separate agent.*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): increased mortality, QT prolongation

Appendix D: General Information

For MDR-TB:

- Sirturo should only be used 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 treatment may be initiated in combination with at least 4 other drugs to which the patient's MDR-TB isolate is likely susceptible.
- Laboratory confirmation of multi-drug resistant TB must show TB with an isolate showing genotypic or phenotypic resistance to isoniazid and rifampin.

For MDR-TB or XDR-TB with pretomanid:

- CDC Centers of Excellence for TB: https://www.cdc.gov/tb/education/tb_coe/default.htm
- Pretomanid should only be used in combination with Sirturo and linezolid.
- Dosing of the combination regimen of pretomanid, Sirturo, and linezolid can be extended beyond 26 weeks if necessary, to a maximum of 9 months, in patients with delayed culture conversion.
    - Delayed culture conversion: two consecutive negative sputum cultures following an initial positive culture.
- Laboratory confirmation of multi-drug resistant TB must show TB with an isolate showing genotypic or phenotypic resistance to isoniazid and rifampin.
- Laboratory confirmation of extensively drug resistant TB must show TB with an isolate showing genotypic or phenotypic resistance to isoniazid, rifampin, fluoroquinolones, as well as second-line injectable agents such as aminoglycosides or capreomycin.

- Linezolid starting dose of 1,200 mg daily for 26 weeks may be managed as follows:
  - Adjusted to 600 mg daily and further reduced to 300 mg daily as necessary for adverse reactions of myelosuppression, peripheral neuropathy, and optic neuropathy.
  - Doses of the regiment missed for safety reasons can be made up at the end of treatment; does of linezolid alone missed due to adverse reactions should not be made up.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MDR-TB	Weight ≥ 30 kg: 400 mg PO QD for the first 2 weeks, followed by 200 mg PO three times per week (with at least 48 hours between doses) for 22 weeks (total duration of 24 weeks). Weight 15 to 29 kg: 200 mg PO QD for the first 2 weeks, followed by 100 mg PO three times per week (with at least 48 hours between doses) for 22 weeks (total duration of 24 weeks). Situro should be administered by directly observed therapy (DOT)	Weight ≥ 30 kg: 400 mg/dose Weight 15 to 29 kg: 200 mg/dose
MDR-TB or XDR-TB with pretomanid	Administer in combination with pretomanid and linezolid in a directly observed therapy (DOT) setting. • Sirturo: 400 mg PO QD for the first 2 weeks, followed by 200 mg PO three times per week (with at least 48 hours between doses) for 24 weeks (total duration of 26 weeks). • Pretomanid: 200 mg PO QD for 26 weeks. • Linezolid: 1,200 mg PO QD for 26 weeks. *600 mg for 15-17 years of age Patients 17 years of age or older may continue treatment with Sirturo and pretomanid without linezolid if the patient has previously received a total daily dose of linezolid 1,200 mg for at least 4 weeks.	400 mg/dose

VI. Product Availability

Tablet: 20 mg, 100 mg

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy Created	01/2020	
1Q 2021 annual review: updated for pediatric extension from 12 years old or 30 kg to 5 years of age or 15 kg for MDR-TB without Pretomanid per revised prescribing information; for requests in combination with Pretomanid, revised prescriber requirement from infectious disease specialist to an expert in the treatment of tuberculosis; references reviewed and updated	01/2021	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2022 annual review: clarified expert in the treatment of tuberculosis to include state or county public health department, specialists affiliated with any of the four TB Centers of Excellence as designated by the CDC, or ID specialists managing TB clinics; references reviewed and updated.	01/2022	
1Q 2023 annual review: for use without Pretomanid added requirement for weight ≥ 15 kg per prescribing information; for use with Pretomanid lowered age requirement from 17 to 15 years per updated WHO 2022 guidance, added alternative option if there is no documented fluoroquinolone resistance for off-label use when prescribed in combination with moxifloxacin, clarified approval duration from 6 months to 26 weeks; for continued therapy reinforced therapy duration requirements that were previously only referenced in the approval duration; references reviewed and updated.	01/2023	