Prior Authorization Review Panel

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CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 02/01/2021**
Policy Number: PA.CP.PMN.212	**Effective Date: 01/2020** **Revision Date: 01/2021**
Policy Name: Bedaquiline (Sirturo)	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL** - *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

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

Name of Authorized Individual (Please type or print): **Auren Weinberg, MD**	**Signature of Authorized Individual:** 

Clinical Policy: Bedaquiline (Sirturo)

Reference Number: PA.CP.PMN.212
Effective Date: 01/2020
Last Review Date: 01/2021

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.

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 health plans affiliated with 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;
3. Age ≥ 5 years;
4. Prescribed in combination with at least 3 other anti-tuberculosis agents (*Appendix B*);
5. 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;
3. Age ≥ 17 years;
4. Prescribed in combination with pretomanid and linezolid;
   **Prior authorization may be required for pretomanid and linezolid.*
5. 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: 6 months

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. 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 a dose increase, new dose does not exceed 200 mg three times per week.

Approval duration: up to a total treatment duration of 6 months (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
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
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.
- Sirturo was approved under accelerated approval based on time to sputum culture conversion. Continued approval for its indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- 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	Weight ≥ 30 kg: 400 mg/dose Weight 15 to 29 kg: 200 mg/dose

Indication	Dosing Regimen	Maximum Dose
	(with at least 48 hours between doses) for 22 weeks (total duration of 24 weeks). Situro should be administered by directly observed therapy (DOT)	
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. Patients 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

1. Sirturo Prescribing Information. Titusville, NJ: Janssen Therapeutics; May 2020. Available at: https://www.sirturo.com/. Accessed November 3, 2020.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://www.clinicalpharmacology-ip.com/. Accessed November 3, 2020.
3. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. 2013; 62(RR09):1-12. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e. Accessed November 3, 2020.
4. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance 2013. Available at: https://www.ncbi.nlm.nih.gov/books/NBK154134/pdf/Bookshelf_NBK154134.pdf. Accessed November 3, 2020.
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6. Pretomanid Prescribing Information. Hyderabad, India: Mylan; August 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf. Accessed November 3, 2020.

7. FDA Briefing Document for Pretomanid tablet, 200mg. Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC): New York, NY: June 6, 2019. Available at: https://www.fda.gov/media/127592/download. Accessed November 3, 2020.
8. Pretomanid: Sponsor Briefing Document Antimicrobial Drugs Advisory Committee. New York, NY: June 6, 2019. Available at: https://www.fda.gov/media/127593/download. Accessed November 3, 2020.
   Nahid P, Mase SR, Migliori GM, et al. Treatment of Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. Am J Respir Crit Care Med. Nov 15, 2019. 200 (10): e93–e142.

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	