RXADVANCE
2 Park Central Drive
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Clinical Policy Title:	bedaquiline
Policy Number:	RxA.490
Drug(s) Applied:	Sirturo®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All line of Business

Background

Bedaquiline (Sirturo®) is a diarylquinoline antimycobacterial drug. It is indicated as part of as part of combination therapy in 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.

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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
bedaquiline (Sirturo®)	MDR-TB	Weight ≥ 30 kg: 400 mg PO once daily 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 once daily 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). Take with food. 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 once daily for the	400 mg/dose

		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 once daily for 26 weeks. • Linezolid: 1,200 mg PO once daily 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.	

Dosage Forms

- Tablet: 20 mg, 100 mg

Clinical Policy

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

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 (*see Appendix B*);
5. Documented resistance to fluoroquinolones, unless contraindicated or clinically significant adverse effects are experienced;
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
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

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 infectious disease specialist or a pulmonologist;
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
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

II. Continued Therapy

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

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
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
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

B. Multi-Drug Resistant Tuberculosis with Pretomanid (must meet all):

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Member continues to receive pretomanid;
4. Member has previously received at least 4 weeks of linezolid 1,200 mg per day;
5. If request is for a dose increase, new dose does not exceed 200 mg three times per week.

Approval duration
Commercial: 6 months (9 months if evidence of delayed culture conversion)
Medicaid: 6 months (9 months if evidence of delayed culture conversion)
HIM: 6 months (9 months if evidence of delayed culture conversion)

III. Appendices

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	Maximum Dose
amikacin/kanamycin	15 mg/kg IM or IV once daily or 25 mg/kg PO three times weekly	15 mg/kg/day

Capreomycin	15 mg/kg IM or IV once daily or 25 mg/kg PO three times weekly	1,000 mg/day
Cycloserine	10 to 15 mg/kg PO once or twice daily	1,000 mg/day
Ethambutol	Follow weight-based dosing in prescribing information	4,000 mg/dose
Ethionamide	10 to 20 mg/kg PO once or twice daily	1,000 mg/day
imipenem-cilastatin*	1,000 mg IV twice daily	2,000 mg/day
Levofloxacin	500 to 1,000 mg PO or IV once daily	1,000 mg/day
Linezolid	600 mg PO or IV once daily	600 mg/day
meropenem*	2,000 mg IV two or three times daily	6,000 mg/day
Moxifloxacin	400 mg PO or IV once daily	400 mg/day
para-aminosalicylic acid	8 to 12 g PO two or three times daily	12 g/day
Pyrazinamide	Follow weight-based dosing in prescribing information	4,000 mg/dose
Streptomycin	15 mg/kg IM or IV once daily or 25 mg/kg PO three times weekly	20 mg/kg/day
Pretomanid	200 mg PO once daily for 26 weeks	200 mg/day
Linezolid	1,200 mg PO once daily	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

- 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.
- Hepatotoxicity may occur with use of Sirturo®. Monitor liver-related laboratory tests. Discontinue Sirturo® if evidence of liver injury occurs.

For MDR-TB or XDR-TB with pretomanid:

- 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 regimen missed for safety reasons can be made up at the end of treatment; dose of linezolid alone missed due to adverse reactions should not be made up.

References

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5. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1. Accessed September 7, 2020.
6. Pretomanid Prescribing Information. Hyderabad, India: Mylan; August 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf. Accessed September 7, 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 September 7, 2020.
8. Pretomanid: Sponsor Briefing Document Antimicrobial Drugs Advisory Committee. New York, NY: June 6, 2019.

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy was established	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Line of business policy applies was updated to all lines of business. 2. Background and dosing information table was updated to include more specific indications and dosing regimen. 3. Initial Approval Criteria and continued therapy was updated to include more specific criteria. 4. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. Approval duration was updated in initial as well clinical approval criteria. 6. Appendix A was updated to add XDR-TB. 7. Appendix B was updated to add pretomanid and linezolid. 8. Appendix D was updated to include general information about dosing regimen with pretomanid. 9. References were updated.	09/07/2020	12/07/2020