Clinical Policy: Bedaquiline (Sirturo)

Reference Number: CP.PMN.212
Effective Date: 09.04.18
Last Review Date: 02.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® 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, 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 (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Multi-Drug Resistant Tuberculosis without Pretomanid (must meet all)**:**
1. Member meets one of the following (a or b):

a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

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. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BPaL: bedaquiline, pretomanid, and linezolid
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
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
pretomanid	200 mg PO QD for 26 weeks.	200 mg/day
linezolid	600 - 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	Weight ≥ 30 kg: 400 mg/dose

Indication	Dosing Regimen	Maximum Dose
	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). Sirturo should be administered by directly observed therapy (DOT)	Weight 15 to 29 kg: 200 mg/dose
MDR-TB or XDR-TB with pretomanid	Administer in combination with pretomanid and linezolid (BPaL regimen) 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: 600 mg PO QD for 26 weeks*. 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. ** Treatment with the BPaL regimen can be extended beyond 26 weeks up to 9 months (39 weeks) based on 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.*	400 mg/dose

VI. Product Availability

Tablet: 20 mg, 100 mg

VII. References

1. Sirturo Prescribing Information. Titusville, NJ: Janssen Therapeutics; September 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204384s017lbl.pdf. Accessed October 20, 2023.
2. Clinical Pharmacology [database online]. Elsevier, Inc. Updated periodically. Available at: https://www.clinicalkey.com/pharmacology/. Accessed October 30, 2023.
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 October 25, 2022.

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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 September 23, 2021.
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 October 30, 2023.
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 October 30, 2023.
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11. Provisional CDC Guidance for the Use of Pretomanid as part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease. Updated May 4, 2023. Available at: https://www.cdc.gov/tb/topic/drtb/bpal/. Accessed October 30, 2023.
12. WHO-Rapid communication: Key changes to the treatment of drug-resistant tuberculosis. May 2022. Available at: https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2. Accessed October 30, 2023.
13. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. 18 March 2022. Available at: https://www.who.int/publications/i/item/9789240046764. Accessed October 30, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Criteria added for treatment of multi-drug resistant and extensively drug resistant TB with pretomanid; Added general information regarding all oral combination regimen of pretomanid, bedaquiline, and linezolid based on FDA briefing document; references reviewed and updated.	09.24.19	02.20
RT4: 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.	06.02.20	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: added Commercial line of business, for requests in combination with Pretomanid revised prescriber requirement from infectious disease specialist to an expert in the treatment of tuberculosis; added expert in the treatment of tuberculosis as an additional specialist prescriber option to Section IA in addition to infectious disease specialist and pulmonologist; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	11.02.20	02.21
Removed requirement for fluoroquinolone resistance for use without pretomanid to align with IDSA/WHO 2019 guidelines for MDR-TB; 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.	04.06.21	05.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	09.23.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.05.22	
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.	10.25.22	02.23
1Q 2024 annual review: no significant changes; updated linezolid dosing from 1,200 mg to 600 mg per updated CDC recommendations; references reviewed and updated.	10.20.23	02.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.