

Clinical Policy: Bedaquiline (Sirturo)

Reference Number: CP.PMN.212

Effective Date: 09.04.18

Last Review Date: 02.20

Line of Business: 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 (12 to less than 18 years of age and weighing at least 30 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 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 or a pulmonologist;
3. Age \geq 12 years;
4. Prescribed in combination with at least 3 other anti-tuberculosis agents (*Appendix B*);
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: 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 infectious disease specialist;
3. Age \geq 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 for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 200 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 Centene benefit or member has previously met initial approval criteria;
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: 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 Centene benefit and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is

NOT authorized): HIM.PHAR.21 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 – HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid or evidence of coverage documents.

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	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). Sirturo should be administered by directly observed therapy (DOT)	400 mg/dose

Indication	Dosing Regimen	Maximum Dose
MDR-TB or XDR-TB with pretomanid	Administer in combination with pretomanid and linezolid in a directly observed therapy (DOT) setting. <ul style="list-style-type: none"> • 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: 100 mg

VII. References

1. Sirturo Prescribing Information. Titusville, NJ: Janssen Therapeutics; August 2019. Available at: <https://www.sirturo.com/>. Accessed August 16, 2019.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: <http://www.clinicalpharmacology-ip.com/>. Accessed August 22, 2019.
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 August 5, 2019.
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 August 5, 2019.
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 August 5, 2019.
6. Pretomanid Prescribing Information. Hyderabad, India: Mylan; August 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf. Accessed September 6, 2019.
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 6, 2019.
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 September 6, 2019.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adapted from previously approved policy HIM.PA.18 (to be retired); added HIM and Medicaid lines of business; added additional therapy options to Appendix B (alphabetized table) based on 2019 WHO guidelines and commercially available in the US (ethambutol, imipenem-cilastatin, linezolid, meropenem); updated FDA-approved age limit to 12 years of age and older; references reviewed and updated.	08.05.19	11.19
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

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.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.

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