Clinical Policy: Osilodrostat (Isturisa)

Reference Number: CP.PHAR.487
Effective Date: 09.01.20
Last Review Date: 08.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Osilodrostat (Isturisa®) is a cortisol synthesis inhibitor.

FDA Approved Indication(s)

Isturisa is indicated for the treatment of endogenous hypercortisolemia in adults with Cushing's syndrome (CS) for whom surgery is not an option or has not been curative.

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 Isturisa is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cushing's Syndrome (must meet all)**:**

1. Diagnosis of CS;
2. Prescribed by or in consultation with an endocrinologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Surgery has not been curative;
   b. Member is not eligible for surgery;
5. Dose does not exceed 30 mg twice daily.

Approval duration: 6 months

B. 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. Cushing's Syndrome (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 (*see Appendix D*);
3. If request is for a dose increase, new dose does not exceed 30 mg twice daily.

Approval duration: 12 months

B. 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

CS: Cushing's syndrome
FDA: Food and Drug Administration
UFC: urinary free cortisol

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- Treatment response for CS may be defined as reduction in 24-hour urinary free cortisol (UFC) levels and/or improvement in signs or symptoms of the disease. Maximum UFC reduction is typically seen by two months of treatment.
- Across sampled U.S. laboratories (Mayo Clinic Laboratories, LabCorp, Quest Diagnostics), 24-hour UFC adult reference values range from 3 to 64 mcg/24 h. The American Association of Neurological Surgeons notes that UFC levels higher than 50-100 mcg/24 h in adults suggest the presence of CS. In this context, the Endocrine Society notes that 24-hour UFC levels may range from more than 5 times normal in severe cases to as low as 1.5 times normal in relatively mild cases.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CS	<u>Recommended Dosage, Titration, and Monitoring</u> • Initiate dosing at 2 mg orally twice daily, with or without food. • Initially, titrate the dosage by 1 to 2 mg twice daily, no more frequently than every 2 weeks based on the rate of cortisol changes, individual tolerability and improvement in signs and symptoms of CS. If a patient tolerates Isturisa dosage of 10 mg twice daily and continues to have elevated 24-hour urine free cortisol (UFC) levels above upper normal limit, the dosage can be titrated further by 5 mg twice daily every 2 weeks. Monitor cortisol levels from at least two 24-hour urine free cortisol collections every 1-2 weeks until adequate clinical response is maintained. • The maintenance dosage of Isturisa is individualized and determined by titration based on cortisol levels and patient's signs and symptoms. • The maintenance dosage varied between 2 mg and 7 mg twice daily in clinical trials. The maximum recommended maintenance dosage of Isturisa is 30 mg twice daily. • Once the maintenance dosage is achieved, monitor cortisol levels at least every 1-2 months or as indicated. <u>Dosage Interruptions and Modifications</u> • Decrease or temporarily discontinue Isturisa if urine free cortisol levels fall below the target range, there is a rapid decrease in cortisol levels, and/or patients report symptoms	60 mg/day

Indication	Dosing Regimen	Maximum Dose
	of hypocortisolism. If necessary, glucocorticoid replacement therapy should be initiated. • Stop Isturisa and administer exogenous glucocorticoid replacement therapy if serum or plasma cortisol levels are below target range and patients have symptoms of adrenal insufficiency. • If treatment is interrupted, re-initiate Isturisa at a lower dose when cortisol levels are within target ranges and patient symptoms have been resolved.	

VI. Product Availability

Tablets: 1 mg, 5 mg

VII. References

1. Isturisa Prescribing Information. Lebanon, NJ: Recordati Rare Disease, Inc.; April 2025. Available at: https://isturisa.com/patient. Accessed April 28, 2025.
2. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015; 100:2807.
3. Cushing's syndrome/disease. American Association of Neurological Surgeons. Available at https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Cushings-Disease. Accessed May 20, 2025.
4. Biller BMK, Newell-Price J, Fleseriu M, et al. OR16-2 Osilodrostat treatment in Cushing's disease (CD): Results from a phase III, multicenter, double-blind, randomized withdrawal study (LINC 3). Journal of the Endocrine Society. 2019; 3(Suppl 1): OR16-2, https://doi.org/10.1210/js.2019-OR16-2.
5. Fleseriu M, Pivonello R, Young J, et al. Osilodrostat, a potent oral 11b-hydroxylase inhibitor: 22-week, prospective, phase II study in Cushing's disease. Pituitary. 2016; 19: 138-148. DOI 10.1007/s11102-015-0692-z.
6. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021 Dec; 9(12): 847-875.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2021 annual review: no significant changes; modified HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	04.05.21	08.21
3Q 2022 annual review: no significant changes; references reviewed and updated.	05.04.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
3Q 2023 annual review: no significant changes; references reviewed and updated.	04.14.23	08.23
3Q 2024 annual review: no significant changes; references reviewed and updated.	05.14.24	08.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2025 annual review: RT4: revised FDA Approved Indication(s) to reflect expanded approval in Cushing's syndrome (previously only Cushing's disease) and modified criteria to reflect updated labeling language; removed 10 mg tablet strength as it is no longer on market; references reviewed and updated.	04.28.25	08.25

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.