Clinical Policy: Osilodrostat (Isturisa)

Reference Number: PA.CP.PHAR.487
Effective Date: 07/2020
Last Review Date: 07/2025

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 PA Health & Wellness® 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 not 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

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. Cushing's Disease (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. PHARM.01) applies;
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. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA. PHARM.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
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 ofCS. 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	60 mg/day

Indication	Dosing Regimen	Maximum Dose
	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. Dosage Interruptions and Modifications • 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 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
Policy created	07/2020
3Q 2021 annual review: no significant changes; references reviewed and updated.	07/2021
3Q 2022 annual review: no significant changes; references reviewed and updated.	07/2022
3Q 2023 annual review: no significant changes; references reviewed and updated.	07/2023
3Q 2024 annual review: no significant changes; references reviewed and updated.	07/2024
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.	07/2025