LOUISIANA BLUE

osilodrostat (Isturisa®)

Policy # 00721
Original Effective Date: 12/14/2020
Current Effective Date: 12/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider osilodrostat (Isturisa®)‡ for the treatment of endogenous hypercortisolemia in adults with Cushing's syndrome to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for osilodrostat (Isturisa) will be considered when the following criteria are met:

- Patient has a diagnosis of endogenous Cushing's syndrome; AND
  Note: Cushing's disease is included within Cushing's syndrome.
- Patient is 18 years of age or older; AND
  - Patient is not a candidate for pituitary surgery, OR surgery has not been curative for the patient; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) at least ONE alternative treatment option unless there is clinical evidence or patient history that suggests the alternativ treatment options will be ineffective or cause an adverse reaction to the patient. Alternative treatment options include pasireotide (Signifor®)‡, generic cabergoline, generic ketoconazole, metyrapone (Metopirone®)‡, or mitotane (Lysodren®)‡.
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of osilodrostat (Isturisa) when the patient has not tried and failed at least one alternative treatment option (e.g., Signifor, generic cabergoline, generic ketoconazole, Metopirone, or Lysodren) to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of osilodrostat (Isturisa) when the patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Isturisa is a cortisol synthesis inhibitor indicated for the treatment of endogenous hypercortisolemia in adults with Cushing's syndrome for whom surgery is not an option or has not been curative. Isturisa inhibits the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland to reduce excess cortisol. The recommended initial dose is 2 mg administered orally twice daily, and the maintenance dose is determined by titration based on cortisol levels and the patient's signs and symptoms. The maximum recommended maintenance dose is 30 mg twice daily.

Endogenous Cushing's syndrome is a rare disorder characterized by excessive levels of cortisol in the body, known as hypercortisolism. The clinical presentation of Cushing's syndrome is highly variable and may include signs and symptoms such as hypertension, menstrual irregularities, diabetes, weight gain, acne, characteristic facial rounding ("moon face"), truncal obesity, and slender extremities. Cushing's syndrome may be attributed to either excessive corticotropin (ACTH) production (ACTH-dependent Cushing syndrome) or by autonomous adrenal cortisol secretion (ACTH-independent Cushing syndrome). Cushing's disease is a subset of Cushing's syndrome caused by an adrenocorticotropic hormone (ACTH)-dependent pituitary adenoma. Treatment should be directed, whenever possible, at the primary cause of the syndrome. The 2015 Endocrine Society Guidelines recommend surgical removal of the tumor causing the excess cortisol, unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid levels. In patients with ACTH-dependent Cushing's syndrome who underwent non-curative surgery or for whom surgery was not possible, guidelines recommend several second-line therapies such as repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy. The guidelines recommend drugs from three classes for patients after transsphenoidal surgery: 1) Steroidogenesis inhibitors such as ketoconazole, metyrapone, mitotane, and etomidate, 2) pituitary-directed medical therapies such as cabergoline and pasireotide, and 3) the glucocorticoid receptor (GR-II) antagonist, mifepristone. Each of these classes have specific risks and benefits that depend on etiology and patient characteristics. Isturisa is the first cortisol synthesis inhibitor to be approved for this indication, but it has not been studied in comparison to these standard therapies or addressed in clinical guidelines.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Isturisa is approved for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. In April 2025, Isturisa was approved for the treatment of endogenous hypercortisolemia in adults with Cushing's syndrome for whom surgery is not an option or has not been curative.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The safety and efficacy of Isturisa was evaluated in 2 multicenter clinical studies, Study 1 and Study 2, in adults with persistent or recurrent Cushing's disease despite pituitary surgery or de novo patients for whom surgery was not indicated or who had refused surgery.

Study 1

The safety and efficacy of Isturisa was assessed in a 48 week, multicenter study that consisted of four study periods as follows:

- Period 1: 12-week, open-label, dose titration period
- Period 2: 12-week, open-label, maintenance treatment period
- Period 3: 8-week, double-blind, placebo-controlled, randomized withdrawal treatment period
- Period 4: open-label treatment period of 14-24 weeks duration.

The trial enrolled Cushing's disease patients with persistent or recurrent disease despite pituitary surgery or de novo patients for whom surgery was not indicated or who had refused surgery. Persistence or recurrence of Cushing's disease was evidenced by the mean of three 24-hour urinary free cortisol (mUFC) measurements >1.5 times the upper limit of normal.

In period 1, 137 patients received the starting dose of 2 mg Isturisa orally twice daily that could be titrated up to a maximum of 30 mg twice daily at no greater than 2-week intervals to achieve a mUFC within the normal range. Individual dosage adjustments were made to keep the mUFC within the normal range (i.e., dose increased if below normal and decreased if above normal).

Out of the patients included in period 1, 130 entered period 2. The daily dose for patients that achieved a mUFC within the normal range in period 1 was maintained during period 2. Patients who did not require further dose increase, tolerated the drug, and had a mUFC ≤ the upper limit of normal (ULN) at week 24 were to be considered responders and eligible to enter period 3.

At week 26, 71 patients were considered responders and were randomized 1:1 to continue receiving Isturisa (n = 36) or switch to placebo (n = 35) for 8 weeks. Patients were stratified at randomization according to dose received at week 24 and history of pituitary irradiation. Patients with mUFC increase >1.5 times the upper limit of normal or who required a dose increase were considered non-responders and discontinued from period 3 but allowed to receive open-label treatment during period 4.

Period 4 included patients who were not eligible for randomization into period 3 (n = 47), patients who were considered non-responders during period 3 (n = 29), and patients who were considered responders during period 3 (n = 41). Open-label treatment with Isturisa continued in these patients until week 48 when patients who maintained clinical benefit on Isturisa had an option to enter an extension period.

The primary efficacy endpoint of the study was to compare the percentage of complete responders at the end of the 8-week randomized withdrawal period (period 3) between patients randomized to continue Isturisa versus the patients switched to placebo. A complete responder for the primary endpoint was defined as a patient who had a mUFC ≤ ULN based on central laboratory result at the end of period 3 and who neither discontinued randomized treatment or the study nor had any dose increase above their week 26 dose. In the Isturisa continuation group, 86% of patients met this endpoint compared to 29% in the placebo group (difference of 57%). This difference was statistically significant with a two-sided confidence interval of (38,76).

Study 2

The safety and efficacy of Isturisa was assessed in a 48-week, multicenter study that consisted of two core study periods as follows:

- Period 1: 12-week, double-blind, placebo-controlled, randomized treatment period with Isturisa or placebo.
- Period 2: 36-week, open-label, treatment period with Isturisa.

Study 2 enrolled 74 patients with Cushing's disease, of whom 73 were treated. Overall, 96% of patients had persistent/recurring Cushing's disease prior to entering the study, of which 88% had undergone previous surgery and 62% of patients had prior medical treatment for Cushing's disease. Persistence or recurrence of Cushing's disease was evidenced by the mUFC > 1.3 x ULN.

Period 1 (Week 1 to 12)

Seventy-three patients received a starting dose of 2 mg twice daily Isturisa or placebo orally twice daily that could be titrated up at approximately 3-week intervals to achieve a mUFC within the normal range, using the following dose escalation sequence: 2 mg twice daily to 5mg twice daily to 10 mg twice daily up to a maximum of 20 mg twice daily, with intermediate doses used if necessary. Individual dose adjustments were based on mUFC and other relevant data (i.e. serum cortisol, ACTH, chemistry, clinical signs and symptoms of adrenal insufficiency, vitals and study drug dose, tolerability). The dose was increased if mUFC was above ULN and was reduced if mUFC was below the lower limit of normal (LLN), or if the patients had signs and/or symptom consistent with adrenal insufficiency and mUFC was in the lower part of the normal range.

Period 2 (Week 13 to 48)

In this period, all patients who were receiving 2 mg twice daily or more during the double-blind period restarted Isturisa at a dose of 2 mg twice daily at Week 12. Patients receiving daily dose < 2 mg twice daily during the 12-week double-blind randomized, placebo-controlled period were to continue treatment with their last dose from Period 1. During Period 2, decisions regarding dose

titration of Isturisa were made by the Investigators based on mUFC values and tolerability using the same dose escalation sequence as in the double-blind period. The maximum dose was 30 mg twice daily. Treatment with Isturisa continued in these patients until Week 48 when patients had an option to enter an extension period of an additional 48 weeks.

The primary efficacy endpoint Study 2 was the complete response status at Week 12. A complete responder was defined as a patient who has mUFC ≤ ULN (based on central laboratory result) at Week 12 who neither discontinued during the placebo-controlled period nor had a missing mUFC assessment at Week 12. At the end of Period 1, the percentage of complete responders for the primary endpoint was 77% and 8% in the Isturisa and placebo groups, respectively.

References

1. Isturisa [package insert]. Recordati Rare Diseases, Inc. Lebanon, NJ. Updated July 2025.
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3. Isturisa Prior Authorization Policy. Express Scripts. May 2020.
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5. Reincke M, Fleseriu M. Cushing syndrome: a review. *JAMA*. 2023;330(2):170-181.
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;9(12):847-875.
7. Nieman, LK (2024). Primary therapy of Cushing disease: Transsphenoidal surgery and pituitary irradiation. Lacroix A & Rubinow K (Ed.), *UpToDate*. Retrieved October 17, 2025, from www.uptodate.com/contents/primary-therapy-of-cushing-disease-transsphenoidal-surgery-and-pituitary-irradiation.

Policy History

Original Effective Date: 12/14/2020
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11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. New policy.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2024	Medical Policy Committee review
11/13/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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11/06/2025 Medical Policy Committee review
11/12/2025 Medical Policy Implementation Committee approval. Updated criterion requiring a diagnosis of Cushing's disease to requiring a diagnosis of endogenous Cushing's syndrome based on the label update. Updated background section.
Next Scheduled Review Date: 11/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.