osilodrostat (Isturisa®)

Policy # 00721
Original Effective Date: 12/14/2020
Current Effective Date: 12/11/2023

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 Cushing's disease 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 Cushing's disease; AND
- 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 for Cushing's disease unless there is clinical evidence or patient history that suggests the alternative treatment options will be ineffective or cause an adverse reaction to the patient. Alternative treatment options for Cushing's disease include pasireotide (Signifor®)‡, generic cabergoline, generic ketoconazole, metyrapone (Metopirone®)‡, or mitotane (Lysodren®)‡.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

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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 for Cushing's disease (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 adults with Cushing's disease for whom pituitary 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.

Cushing's disease is a subset of Cushing's syndrome caused by an adrenocorticotropic hormone (ACTH)-dependent pituitary adenoma. This tumor causes excess cortisol which results in a variety of signs and symptoms including high blood pressure, diabetes, weight gain, acne, truncal obesity, and others. Goals of treatment include normalizing the cortisol excess, avoiding and reversing the clinical features, and controlling the disease long term. While surgery to remove the pituitary adenoma is the primary treatment for Cushing's disease, it is not always possible or successful. Medications used for adjuvant treatment in patients with persistent disease despite surgical interventions include steroidogenesis inhibitors such as ketoconazole or metyrapone and pituitary-directed agents such as cabergoline and pasireotide. 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.

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 federal regulations, other plan medical policies, and accredited national guidelines.

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 ≤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≤ upper limit of normal 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).

References

1. Isturisa [package insert]. Recordati Rare Diseases, Inc. Lebanon, NJ. March 2020.
2. Isturisa Drug Evaluation. Express Scripts. May 2020.
3. Isturisa Prior Authorization Policy. Express Scripts. May 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.

Next Scheduled Review Date: 11/2024

*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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.

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.