Isturisa (osilodrostat)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Isturisa (osilodrostat) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Isturisa (osilodrostat) is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

POLICY

Documentation

Submission of the following information is necessary to initiate the prior authorization review:

1. For initial requests:
    - A confirmed diagnosis of Cushing's disease that is persistent or recurrent as evidenced by all of the following:
        - Mean urinary free cortisol (mUFC) level that is at least 1.3 x the upper limit of normal (ULN) measured over three 24 hour measurements (ULN = 50 mcg/24 hours or 145 nmol/24 hours)
        - Morning plasma adrenocorticotropic hormone (ACTH) above Lower Limit of Normal
        - Confirmation of pituitary source of excess ACTH as defined by one or more of the following:
            i. Histopathologic confirmation of an ACTH-staining adenoma in members who have had prior pituitary surgery
            ii. MRI confirmation of pituitary adenoma > 6 mm

iii. For members with a tumor ≤ 6mm, a confirmatory bilateral inferior petrosal sinus sampling (BIPSS) test with a pre-dose central to peripheral ACTH gradient > 2 or a post-dose central to peripheral ACTH gradient > 3 after either corticotropin-releasing hormone (CRH) or desmopressin (DDAVP) stimulation

- Documentation supporting one of the following
  - Surgery to remove the corticotropin [ACTH]-secreting pituitary tumor tumor did not result in normalization of circulating cortisol levels
  - Surgical removal is contraindicated or member is not a candidate for surgery

2. For continuation of therapy:
   - Documentation supporting the clinical benefit of Isturisa therapy (i.e., lower urinary free cortisol levels since the start of therapy AND improvement in signs and symptoms of the disease)

Exclusion

Coverage will not be provided for members with other causes of Cushing's Syndrome (e.g., ectopic ACTH secretion or ACTH-independent [adrenal] Cushing's syndrome) aside from Cushing's Disease which is specifically caused by a pituitary adenoma.

Criteria for Initial Approval

A. Isturisa (osilodrostat) may be considered **medically necessary** for the treatment of adults with Cushing's disease when all of the following criteria are met:
   1. A confirmed diagnosis of Cushing's disease that is persistent or recurrent
   2. Member has had surgery that was not curative OR member is not a candidate for surgery
   3. Prescribed by, or in consultation with, a board-certified endocrinologist.
   4. Member has failed at least ONE or has a contraindication or medically justifiable reason that precludes the use of ALL the following oral drug therapies:
      a. pasireotide
      b. ketoconazole
      c. cabergoline
      d. metyrapone
      e. mitotane

Approval will be for **6 months**

Continuation of Therapy

A. Isturisa (osilodrostat) may be considered **medically necessary** for the continued treatment of adults with Cushing's disease when all of the following criteria are met:
   1. The member has achieved or maintained a positive clinical benefit to therapy defined as having lower urinary free cortisol levels AND an improvement in signs and symptoms of the disease since the start of therapy
   2. The member continues to be seen by an endocrinologist or is in consultation with an endocrinologist

Approval will be for **12 months**

Isturisa (osilodrostat) is considered **not medically necessary** for members who do not meet the criteria set forth above.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits

The standard limit is designed to allow a quantity sufficient for the most common uses of the medication. The recommended dosing parameters for all FDA-approved indications fall within the standard limits.

Medication	Standard Limit	FDA-recommended dosing
Isturisa (osilodrostat) 1 mg tablet (a carton contains three blister packs of 20 tablets)	240 tablets per 30 days	Starting dose: 2 mg orally twice daily Titrate dose based on rate of cortisol changes, individual tolerability and improvement in signs and symptoms of Cushing's disease to a maximum dose of 30 mg twice daily.
Isturisa (osilodrostat) 5 mg tablet (a carton contains three blister packs of 20 tablets)	360 tablets per 30 days	
Isturisa (osilodrostat) 10 mg tablet (a carton contains three blister packs of 20 tablets)	180 tablets per 30 days	

CLINICAL RATIONALE

Cushing's syndrome is a collection of clinical signs and symptoms that are the result of elevated plasma glucocorticoid levels. Cushing's syndrome can be due to exogenous or endogenous sources. Exogenous Cushing's syndrome is typically caused by the administration of glucocorticoids, while Cushing's disease, or pituitary corticotroph tumors, accounts for 70% of endogenous Cushing's syndrome cases. Cushing's disease is rare, with an estimated prevalence of almost 40 cases per million individuals. Among adults, women are three times more likely to develop Cushing's disease than men, and symptoms typically appear between the third and sixth decades of life. However, Cushing's disease tends to occur at a younger age and with a more severe clinical presentation in male patients.

In Cushing's disease, patients develop an adrenocorticotropic hormone (ACTH)-secreting pituitary tumor, which is typically benign. This autonomous ACTH overproduction does not respond to regulation from the hypothalamic-pituitary-adrenal axis feedback loop, and as a result, an excess amount of cortisol is secreted from the adrenal glands.

The 2015 Endocrine Society guidelines for the treatment of Cushing's syndrome recommend complete surgical resection of the primary lesion(s) underlying Cushing's disease, unless surgery is not possible or unlikely to significantly reduce glucocorticoid excess. For patients who underwent a noncurative surgery or for whom surgery was not possible, second-line treatment options include additional surgeries, radiotherapy, and pharmacological therapy. Of the pharmacological treatment options, cabergoline and Signifor (pasireotide) are recommended treatment options for patients with Cushing's disease who are not surgical candidates or who have persistent disease following surgery, while ketoconazole, Metopirone (metyrapone), Lysodren (mitotane), and Amidate (etomidate) are recommended as second-line treatment options following surgery with or without radiotherapy in patients with Cushing's disease. Mifepristone is recommended in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after surgery.

Adrenal enzyme inhibitors (i.e., ketoconazole and metyrapone) are the most commonly used drugs, but adrenolytic agents (i.e. mitotane), drugs that target a pituitary or ectopic tumor (e.g., pasireotide, cabergoline, chemotherapy or immunotherapy), and glucocorticoid-receptor antagonists (i.e. mifepristone) also have been studied and used. Only pasireotide, osilodrostat, and mifepristone have an FDA approved indication for Cushing's disease or syndrome. Note: Metopiron (metyrapone) is not commercially available in the U.S. and must be obtained from HRA Pharma via special allocation only.

Isturisa (osilodrostat) is a cortisol synthesis inhibitor indicated for the treatment of adult patients with Cushing's disease for whom primary surgery is not an option or has not been curative. The approval of

Isturisa (osilodrostat) was supported by the double-blind, placebo-controlled, randomized withdrawal period of a four-period, phase III, multicenter LINC-3 trial (N = 137 for initial enrollment; N = 71 for randomized withdrawal period). The primary endpoint was the proportion of responders at the end of the randomized withdrawal period, which was defined as patients with mean UFC ≤ ULN and with no discontinuation or Isturisa (osilodrostat) dose. In the study, Isturisa was superior to placebo for the proportion of responders at week 34 in the randomization withdrawal period (86.1% vs. 29.4%; OR 13.71; 95% CI 3.73 to 53.44; $p < 0.001$) and met the primary endpoint. In terms of safety, the most common adverse events (i.e., ≥ 20% in either arm) in the randomized withdrawal period were nausea, headache, fatigue, nasopharyngitis, glucocorticoid deficiency, arthralgia, back pain, diarrhea, influenza, and asthenia. Of these adverse events, nausea, glucocorticoid deficiency, and asthenia were more common in the Isturisa (osilodrostat) arm than the placebo arm. Of note, the FDA reviewer stated the study design did not allow for proper evaluation of efficacy or safety, due to the exclusion of patients whose disease is more difficult to control as well as carry-over effect of Isturisa (osilodrostat) in the placebo arm during the randomized withdrawal period. Overall, Isturisa (osilodrostat) was effective in maintaining UFC within normal limits, although it was associated with a higher rate of some adverse events, such as glucocorticoid deficiency.

On June 17, 2020, Recordati Rare Diseases Inc. announced study results from their LINC-4 study. LINC-4 is a large randomized, double-blinded, multicenter, 48-week trial with an initial 12-week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients (N=73) with persistent or recurrent Cushing's disease or those with de novo disease who were not candidates for surgery. The primary endpoint is the proportion of patients randomized to osilodrostat and placebo, separately, with a mean urinary free cortisol (mUFC) ≤ULN at the end of the 12-week placebo-controlled period. The key secondary endpoint is the proportion of patients in both arms combined with a mUFC ≤ULN after 36 weeks. The unpublished results demonstrate that a significantly higher proportion of patients receiving osilodrostat achieve normal mUFC, the primary treatment goal for Cushing's disease, after 12 weeks of treatment versus placebo (77% vs 8%; P <0.0001). Improvements in mUFC levels are sustained over 36 weeks of treatment (81% of patients).

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- N/A

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POLICY HISTORY

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