09-J3000-74

Original Effective Date: 10/01/20

Reviewed: 06/14/23

Revised: 07/15/23

Subject: Osilodrostat (Isturisa) tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Cushing's disease is a condition of hypercortisolism that is caused by overproduction of adrenocorticotropic hormone (ACTH) by a pituitary tumor. Tumor resection of the pituitary tumor is the first line treatment although recurrence after surgery may occur. Treatment options following recurrence include repeating surgery, radiotherapy, medication therapy, or bilateral adrenalectomy. Medication therapy may include steroidogenesis inhibitors (e.g., ketoconazole, metyrapone, mitotane), pituitary-directed treatment to inhibit ACTH secretion (e.g. cabergoline, pasireotide) or glucorcorticoid-receptor directed therapy for patients with diabetes mellitus or glucose intolerance (mifepristone). If hypercortisolism persists, complications may include metabolic symptoms, cardiovascular disorders, muscle weakness, neuropsychiatric abnormalities, and osteoporosis.

Osilodrostat (Isturisa) is Food and Drug Administration (FDA) approved for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. Osilodrostat inhibits 11-beta-hydroxylase, an enzyme in the final step of cortisol synthesis in the adrenal gland.

The efficacy of osilodrostat was assessed in a 8-week double-blind, placebo-controlled, multicenter, randomized withdrawal study. There were 2 open label periods prior to the randomized discontinuation period consisting of a total of 24 weeks for dose titration and maintenance treatment, and an additional open-label period following the discontinuation period. Patients with Cushing's disease with persistent or recurrent disease evidenced by the mean of three 24-hour urinary free cortisol (mUFC) greater than 1.5 times the upper limit of normal (ULN) and morning plasma ACTH above the lower limit of normal that had previously had pituitary surgery or those ineligible for surgery were included. Approximately 96% of patients had previously received treatment prior to study entry and 88% had undergone surgery. There were 71 patients who responded to treatment in the open-label period by week 26 and were randomized to continue osilodrostat (n=36) or switch to placebo (n=35) for 8 weeks. The primary

efficacy endpoint was to compare the percentage of complete responders at the end of the 8-week withdrawal period between groups. Complete response was defined in those patients with a mUFC < ULN and did not discontinue or require a dose increase above the week 26 dose. Non-responders were defined as a mUFC > 1.5 ULN or who required a dose increase. At the end of the randomized withdrawal period, the percentage of complete responders was 86% (n=31) and 29% (n=10) for the osilodrostat and placebo groups (rate difference of 57%, p-value <0.001). The complete responder rate following the open-label period at the end of week 24 (preceding the discontinuation period) was a secondary endpoint with 52.6% (n=72/137) complete responders. In an open label period following the discontinuation phase at week 48, 66% (n=91/137) patients had normal mUFC levels. There were variable decreases from baseline for blood pressure, glucose, and weight but the effect from osilodrostat could not be determined because antihypertensive and anti-diabetic medication and dose adjustments were permitted. An increase in pituitary tumor volume by greater than 20% from baseline occurred in 15% (n=21/137) of patients, while a decrease in tumor volume by greater than 20% from baseline was observed in 18% (n=24/137) of patients at week 48. Adverse reactions related to the accumulation of adrenal hormone precursors occurred in 42% of patients which included hypertension, hypokalemia, edema, elevated blood pressure, and elevated testosterone that resulted in hirsutism or acne in females. The most common adverse reactions overall included adrenal insufficiency, fatigue, nausea, headache, edema, nasopharyngitis, vomiting, and arthralgia.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of osilodrostat (Isturisa) **meets the definition of medical necessity** when **ALL** of the following are met:

1. The member has a diagnosis of Cushing's disease
2. The member has persistent or recurrent disease following pituitary surgery **OR** the member is not a candidate for pituitary surgery
3. The member has a mean of three 24 hour urinary free cortisol (UFC) values > 1.5 x upper limit of normal (ULN) – documentation must be submitted
4. The member has an inadequate response, intolerance, or contraindication to at least one alternative oral therapy for the treatment of Cushing's disease (e.g., cabergoline, ketoconazole, metyrapone, mitotane) – documentation must be submitted
5. The member has an inadequate response, intolerance, contraindication to, or is not a candidate for treatment with pasireotide (Signifor, Signifor LAR) – documentation must be submitted
6. ALL of the following baseline tests have been completed:
    a) serum potassium

b) serum magnesium

c) electrocardiogram

7. Osilodrostat will be used as a single agent
8. Osilodrostat will be prescribed by or in consultation with an endocrinologist
9. The dosage does not exceed 30 mg twice a day

Approval duration: 6 months

Continuation of osilodrostat (Isturisa) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has a beneficial response to treatment (e.g., normalization of urinary free cortisol) – documentation must be submitted
2. An authorization or reauthorization has been previously approved for the treatment of Cushing's disease by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
3. The member is not receiving glucocorticoid replacement therapy for the treatment of hypocortisolism
4. Osilodrostat will be used as a single agent
5. Osilodrostat will be prescribed by or in consultation with an endocrinologist
6. The dosage does not exceed 30 mg twice daily

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative - Initiate dosing at 2 mg orally twice daily, with or without food.
- Correct hypokalemia and hypomagnesemia prior to starting treatment. Obtain baseline electrocardiogram (ECG). Repeat ECG within one week after treatment initiation, and as clinically indicated thereafter
- Titration: Initially titrate 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 Cushing's disease. If a patient tolerates 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 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 is 30 mg twice daily. Once the maintenance dosage is achieved, monitor cortisol levels at least every 1-2 months or as indicated.
- Decrease or temporarily discontinue 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 treatment 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 at a lower dose when cortisol levels are within target ranges and patient symptoms have been resolved.

Dose Adjustments

- **Renal Impairment** - Use caution in interpreting urine free cortisol levels in patients with moderate to severe renal impairment, due to reduced urine free cortisol excretion
- **Hepatic Impairment**
  - Moderate hepatic impairment (Child-Pugh B), the recommended starting dose is 1 mg twice daily.
  - Severe hepatic impairment (Child-Pugh C), the recommended starting dose is 1 mg once daily in the evening.
  - More frequent monitoring of adrenal function may be required during dose titration in all patients with hepatic impairment.

Drug Availability

1 mg, 5 mg, 10 mg tablets

PRECAUTIONS:

Boxed Warning

- none

Contraindications

- none

Precautions/Warnings

- Hypocortisolism: Monitor patients closely for hypocortisolism and potentially life-threatening adrenal insufficiency. Dosage reduction or interruption may be necessary
- QTc Prolongation: Perform electrocardiogram in all patients. Use with caution in patients with risk factors for QTc prolongation

- Elevations in Adrenal Hormone Precursors and Androgens: Monitor for hypokalemia, worsening of hypertension, edema, and hirsutism

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

E24.0	Pituitary-dependent Cushing's disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Cushing's syndrome: is a hormone disorder caused by high levels of cortisol in the blood. This can be caused by taking glucocorticoid drugs, or by tumors that produce cortisol or adrenocorticotropic hormone (ACTH) or CRH.

Cushing's disease: when the pituitary gland makes too much of the hormone ACTH. ACTH then signals the adrenal glands to produce cortisol. Tumor of the pituitary gland may cause this condition.

RELATED GUIDELINES:

Levoketoconazole (Recorlev), 09-J4000-17

Pasireotide (Signifor, Signifor LAR) Injection, 09-J1000-94

OTHER

None

REFERENCES:

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5. Nieman LK, Biller B, Findling JW et al. Treatment of Cushing's syndrome: An Endocrine Society Practice Guideline. J Clin Endocrinol Metab. 2015; 100(8): 2907 – 2831.
6. Pivonello R, Fleseriu M, Newell-Price J et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicenter phase III study with a double-blind, randomized withdrawal phase. Lancet Diabetes & Endocrinol.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/14/23.

GUIDELINE UPDATE INFORMATION:

10/01/20	New Medical Coverage Guideline.
07/15/21	Review and revision to guideline consisting of updating references.
09/15/22	Review and revision to guideline; consisting of updating the position statement to include documentation of prior medication use and lab values. Updated references.
07/15/23	Review and revision to guideline; consisting of updating the references.