PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Isturisa® (osilodrostat tablets – Recordati Rare Diseases)

DATE REVIEWED: 05/27/2020

OVERVIEW

Isturisa, a cortisol synthesis inhibitor, is indicated for the treatment of patients ≥ 18 years of age with Cushing's disease for whom pituitary surgery is not an option or has not been curative.[1] Isturisa inhibits cytochrome 11beta-hydroxylase, the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland. The recommended initial dose is 2 mg administered orally twice daily, with or without food. The maintenance dosage of Isturisa is individualized and determined by titration based on cortisol levels and patient's signs and symptoms. Titrate the dosage by 1 to 2 mg twice daily, no more frequently than every 2 weeks based on the rate of cortisol changes (elevated 24-hour urine free cortisol levels above upper normal limit). The maximum recommended maintenance dosage of Isturisa is 30 mg twice daily.

Disease Overview

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). The incidence of endogenous Cushing's syndrome is dependent on the population studied, ranging from 0.7 to 2.4 cases per million population per year and is more common in women than men. Endogenous Cushing's syndrome can be divided into adrenocorticotropic hormone (ACTH) -dependent and ACTH-independent with the majority of cases as ACTH-dependent (80%). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of ACTH-dependent Cushing's syndrome (70%). Other ACTH-dependent causes include ectopic ACTH secretion by a benign or malignant tumor (10%) or rarely ectopic corticotropin-releasing hormone secretion by a tumor. ACTH-independent causes of Cushing's syndrome include adrenal adenoma (10%), adrenal carcinoma (5%), adrenal hyperplasia (1% to 2%), McCune Albright syndrome (1% to 2%) and primary pigmented medullar adrenal disease, including Carney complex (1% to 2%). Patients with Cushing's syndrome exhibit a variety of signs and symptoms such as high blood pressure, diabetes, loss of libido, menstrual disorders, weight gain, hirsutism, acne, easy bruising, purplish skin striae, osteoporosis, muscle weakness, depression, and cognitive impairment as a result of prolonged and inappropriately high exposure of tissue to glucocorticoids. In patients with persistent hypercortisolism, Cushing's syndrome is accompanied by a higher mortality compared to the general population (3.8 to 5 times greater) due to vascular and metabolic comorbidities; therefore, early disease detection is important.

The role of drug therapy in patients with Cushing's syndrome is generally adjunctive and may help to improve the medical status of patients in preparation for surgery, and to control severe hypercortisolism in patients who are acutely ill, or in patients awaiting the effects of radiotherapy.[3-5] Drug therapies act at the hypothalamic-pituitary level and decrease ACTH secretion (e.g., Signifor® [pasireotide injection for subcutaneous use], Signifor® LAR [pasireotide injection for intramuscular use], bromocriptine), at the adrenal level and inhibit cortisol synthesis (steroidgenesis inhibitors [e.g., ketoconazole, Metopirone® {metyrapone capsules}, Lysodren® {mitotane tablets}, etomidate]), or at the peripheral level by competing with cortisol (Korlym® [mifepristone tablets]).[3,6] Pituitary-directed medical treatments are suggested in patients with Cushing's disease who are not surgical candidates or have persistent disease after surgery.[7] Korlym is indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.[8]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Isturisa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Isturisa as well as the monitoring required for adverse events and long-term efficacy, approval requires Isturisa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Isturisa is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cushing's Disease.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's disease; AND
   - **C)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative.
     Note: For patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence.*

Other Uses with Supportive Evidence

2. **Endogenous Cushing's Syndrome.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome; AND
   - **C)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative.
     Note: For patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence.*
   - **D)** The patient meets one of the following (i or ii):
     - **i.** The patient has tried one of ketoconazole tablets, Korlym® (mifepristone tablets), Metopirone® (metyrapone capsules), Lysodren® (mitotane tablets), Signifor® (pasireotide injection for subcutaneous use), or Signifor® LAR (pasireotide injection for intramuscular use) for the treatment of endogenous Cushing's syndrome; OR
     - **ii.** The patient is currently receiving Isturisa.

3. **Endogenous Cushing's Syndrome – Patients Awaiting Surgery.** Approve for 4 months if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

4. **Endogenous Cushing's Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.** Approve for 4 months if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Isturisa not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Isturisa tablets [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; March 2020.
2. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281–293.
3. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. Discov Med. 2012;13(69):171-179.
4. Mazziotti G, Gazzaruso C and Giustina A. Diabetes in Cushing syndrome: basic and clinical aspects. Trends Endocrinol Metab. 2011;22(12):499-506.
5. Rizk A, Honegger J, Milian M and Psaras T. Treatment options in Cushing's disease. Clin Med Insights Oncol. 2012(6):75-84.
6. Arnaldi G and Boscaro M. New treatment guidelines on Cushing's disease. F1000 Med Rep. 2009;1.
7. Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-2831.
8. Korlym™ tablets [prescribing information]. Menlo Park, CA: Corcept Pharmaceuticals; March 2020.