Isturisa (osilodrostat) Prior Authorization with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
12-01-2024

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Isturisa® (osilodrostat) Tablet	Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Cushing's Syndrome	Cushing's syndrome is pathologic hypercortisolism caused by excessive adrenocorticotropic hormone (ACTH) production, or autonomous adrenal production of cortisol. This potentially lethal disorder is associated with significant comorbidities including hypertension, diabetes, coagulopathy, cardiovascular disease, infections, and fractures. As a result, even after cure of hypercortisolism, mortality rates may be increased. Because of this it is important to make the diagnosis as early in the disease course as possible, to prevent additional morbidity and residual disease. Signs and symptoms of Cushing's syndrome are broad and often common among the general population, such as obesity, depression, diabetes, hypertension, or menstrual irregularities. Some features are more discriminatory and unique to Cushing's syndrome, such as reddish-purple striae, plethora, proximal muscle weakness, bruising with no obvious trauma, and unexplained osteoporosis.(2) Cushing's disease is a form of Cushing syndrome. Cushing's disease occurs when a benign tumor in the pituitary gland causes the pituitary gland to produce too much ACTH. Cushing's disease can also occur with diffuse growth of the pituitary gland (pituitary hyperplasia). Pituitary hyperplasia can lead to the release of too much ACTH, which then leads to over-production of cortisol by the adrenal glands.(5) Diagnosis of Cushing's syndrome is often delayed for years, partly because of lack of awareness of the insidious progressive disease process and testing complexity. Screening and diagnostic tests for Cushing's syndrome assess cortisol secretory status: abnormal circadian rhythm with late-night salivary cortisol (LNSC), impaired glucocorticoid feedback with overnight 1 mg dexamethasone suppression test (DST) or low-dose 2-day dexamethasone test (LDDT), and increased bioavailable cortisol with 24-hour urinary free cortisol (UFC). The sensitivity of all tests is higher than 90%; the highest sensitivity rates are obtained with DST and LNSC and the lowest with UFC. Specificity is somewhat lower than sensitivity, with LNSC being the most specific and DST and UFC the least specific. LNSC should not be used in patients with disruption of normal day and night cycle, such as night-shift workers.(6)

	Clinical considerations and recommendations for Cushing's syndrome diagnosis and monitoring of Cushing's disease recurrence:(6)
	
	• If Cushing's syndrome is suspected:
	  o Start with UFC, LNSC or both; DST could be an option if LNSC is not feasible
	  o Multiple LNSC might be easier for patient collection
	
	• If confirming Cushing's syndrome:
	  o Can use any test
	  o UFC (average 2 or 3 collections) above the upper limit of normal – cutoff is assay-specific reference range
	  o LNSC (2 or more tests) above the upper limit of normal – cutoff is assay-specific reference range
	  o DST useful in night-shift workers, not in women on estrogen containing contraceptives – above cutoff of 1.8 mcg/dL
	  o Measuring dexamethasone concentration, with cortisol concentration the morning after 1 mg dexamethasone ingestion improves interpretability
	
	• If Cushing's syndrome due to adrenal tumor is suspected
	  o Start with DST as LNSC has lower specificity in these patients
	
	• Monitoring for recurrence:
	  o Consider which tests were abnormal at initial diagnoses
	  o LNSC most sensitive and should be done annually – above cutoff of 0.27 mcg/dL
	  o DST and UFC usually become abnormal after LNSC (with UFC usually the last to become abnormal)
	  o UFC 1.6 X upper limit of normal
	  o DST above 1.8 mcg/dL
	
	Transsphenoidal surgery is recommended as first-line therapy for patients with Cushing's disease. Remission, typically defined as postoperative serum cortisol concentrations lower than 2 mcg/dL, is seen in approximately 80% of patients with microadenomas and 60% with macroadenomas if the procedure is performed by an experienced surgeon. Patients in remission require glucocorticoid replacement until HPA axis recovery. As remission could be delayed, monitoring until postoperative cortisol nadir can usually identify such cases.(6)
	
	Recurrence after successful pituitary surgery is characterized as the reappearance of clinical and biochemical features of hypercortisolism after initial remission. Published recurrence rates vary between 5% and 35% with half of recurrences appearing within the first 5 years after surgery and half after up to 10 years or more. Compared with use in the initial diagnosis of Cushing's syndrome, LNSC, DST, UFC, and desmopressin tests have a lower sensitivity for recurrence, but specificity is high. Repeat transsphenoidal surgery can be considered in patients with biochemical evidence of recurrent Cushing's disease with visible tumor on MRI.(6)
	
	Medications used for the treatment of Cushing's disease target adrenal steroidogenesis, somatostatin, and dopamine receptors in the pituitary gland, and glucocorticoid receptors.(6)

	• Adrenal steroidogenesis inhibitor agents
	  ○ Ketoconazole: European Medicines Agency (EMA) approved, off-label use in USA
	  ○ Osilodrostat: FDA approved
	  ○ Metyrapone: EMA approved, off-label use in USA
	  ○ Mitotane: EMA approved, off label use in USA
	  ○ Etomidate: Off-label use only
	  ○ Levoketoconazole: EMA indicated, FDA approved
	• Somatostatin receptor ligands
	  ○ Pasireotide: Widely approved
	  ○ Pasireotide long-acting: Widely approved
	• Dopamine receptor agonists
	  ○ Cabergoline: Off-label use only
	• Glucocorticoid receptor blocker
	  ○ Mifepristone: FDA-approved for hyperglycemia associated with Cushing's syndrome.
	
	There are several factors helpful in selection of medical therapy:(6)
	
	• If there is a need for rapid normalization of cortisol adrenal steroidogenesis inhibitors are recommended. Osilodrostat and metyrapone have the fastest action and etomidate can be used in very severe cases (high quality, strong recommendation)
	• In mild disease, if residual tumor is present and there is a potential for tumor shrinkage, consider pasireotide or cabergoline (moderate quality, strong recommendation)
	• If there is a history of bipolar or impulse control disorder, consider avoiding cabergoline (moderate quality, strong recommendation)
	• If an expert pituitary endocrinologist is not available to monitor treatment response, use mifepristone cautiously (low quality, discretionary recommendation)
	• In pregnant women or those desiring pregnancy, consider cabergoline or metyrapone (low quality, strong recommendation), although no Cushing's disease medications are approved for use in pregnancy
	• Drug intolerance or side-effects, as well as concomitant comorbidities such as type 2 diabetes and hypertension should further guide type of medication used (moderate quality, strong recommendation)
	• Consider cost and estimated therapy duration, especially if definitive treatment (i.e., pituitary or adrenal surgery) is planned or while awaiting effects of radiotherapy (low quality, discretionary recommendation)
	
	Adrenal steroidogenesis inhibitors are usually used first given their reliable effectiveness. For patient with mild disease and no visible tumor on MRI, ketoconazole, osilodrostat, or metyrapone are typically preferred. For patients with mild-to-moderate disease and some residual tumor, there might be a preference for cabergoline or pasireotide because of the potential for tumor shrinkage. For patients with severe disease, rapid normalization of cortisol is the most important goal. With osilodrostat and metyrapone, response will typically be seen within hours, and with ketoconazole within a few days.(6)

	Change in treatment should be considered if cortisol levels are persistently elevated after 2-3 months on maximum tolerated doses. If cortisol does not normalize but is reduced or there is some clinical improvement, combination therapy can be considered (low quality, discretionary recommendation). Many experts consider combining ketoconazole with metyrapone or potentially ketoconazole with osilodrostat to maximize adrenal blockade when monotherapy is not effective, or to allow lower doses of both drugs (low quality, discretionary recommendation). Ketoconazole plus cabergoline or pasireotide, and pasireotide plus cabergoline could be rational combinations if there is visible tumor present (low quality, discretionary recommendation). Other combinations that can be used include triplets of cabergoline, pasireotide, plus ketoconazole, and ketoconazole, metyrapone, plus mitotane (low quality, discretionary recommendation).(6) Radiotherapy is primarily used as adjuvant therapy for patients with persistent or recurrent disease after transsphenoidal surgery or for aggressive tumor growth.(6)
Efficacy	Isturisa is a cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland. The safety and efficacy of Isturisa were established in a 48-week, multicenter study that consisted of four study periods.(1) 1. Period 1: Week 1 to 12, open label, dose titration period. 137 patients received a starting dose of 2 mg twice daily that could be titrated up to a max of 30 mg twice daily at no greater than 2-week intervals. Individual dose adjustments were based on mean urinary free cortisol (mUFC). 2. Period 2: Week 13 to 24, open label, maintenance treatment period. 130 of the patients from Period 1 were entered into 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 less than or equal to the upper limit of normal (ULN) at week 24 (end of Period 2) were to be considered responders and eligible to enter the Randomization Withdrawal phase (Period 3). Patients whose mUFC became elevated during Period 2 could have their dose increased further, if tolerated, up to 30 mg twice daily. These patients were considered non-responders and did not enter Period 3 but continued open-label treatment together with the patients who did not achieve normal mUFC at week 12 and were followed for long-term safety and response to treatment. 3. Period 3: Week 26 to 34, double-blind, placebo-controlled, randomized withdrawal treatment period (provided data for primary endpoint). At week 26, 71 patients were considered responders and were randomized 1:1 to continue receiving Isturisa (n=36) or to switch to placebo (n=35) for 8 weeks. Patients were stratified at randomization according to dose received at week 24 (less than or equal to 5 mg twice daily vs 5 mg twice daily) and history of pituitary irradiation (yes/no). Patients were to remain on their assigned treatment and dose throughout Period 3 if mUFC were within the normal range. Blinded dose reduction or temporary discontinuation for safety or tolerability reasons were permitted. Dose increases were not permitted during Period 3. Patients with mUFC increase greater than 1.5 x ULN 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. 4. Period 4: Open label treatment period from weeks 26 or 34 to 48. This period included patients who were not eligible for randomization (n=47) at week 26, 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, as judged by the Investigator, had an option to enter an extension period.

The trial enrolled patients with confirmed persistent or recurrent Cushing's disease despite pituitary surgery or de novo patients for whom surgery was not indicated or who had refused surgery. Inclusion criteria included the following(4):

- Patient's age 18-75 years
- Confirmed Cushing's disease that is persistent or recurrent as evidenced by all of the following criteria being met (i.e., a, b and c):

1. Mean Urine Free Cortisol (mUFC) greater than 1.3 x upper limit of normal [ULN (Mean of three 24-hour urine samples collected preferably on 3 consecutive days, during screening after washout of prior medical therapy for Cushing's disease [if applicable], confirmed by the central laboratory and available before Day 1)], with greater than or equal to 2 of the individual UFC values being greater than 1.3 x ULN
2. Morning plasma ACTH above Lower Limit of Normal
3. Confirmation (based on medical history) of pituitary source of excess ACTH as defined by any one or more of the following three criteria:

a. Histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery OR
b. MRI confirmation of pituitary adenoma greater than 6 mm OR
c. Bilateral inferior petrosal sinus sampling (BIPSS) with either CRH or DDAVP stimulation for patients with a tumor less than or equal to 6mm. The criteria for a confirmatory BIPSS test are any of the following: Pre-dose central to peripheral ACTH gradient greater than 2; Post-dose central to peripheral ACTH gradient greater than 3 after either CRH or DDAVP stimulation

The primary 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 mUFC less than or equal to ULN based on central laboratory result at the end of Period 3 (week 34), and who neither discontinued randomized treatment or the study nor had any dose increase above their week 26 dose. The key secondary endpoint was to assess the complete responder rate at the end of Period 2 (week 24). A complete responder for the key secondary endpoint was defined as a patient with mUFC less than or equal to ULN at week 24 who did not require an increase in dose above the level established at the end of Period 1 (week 12). Patients who were missing mUFC assessment at week 24 were counted as non-responders for the key secondary endpoint.(1)

Primary Endpoint	Isturisa (n=36) n(%)	Placebo (n=34) n(%)	Complete Responder Rate Difference in %
Complete responder rate at the end of the 8-week randomized withdrawal period (Week 34) (95% CI)	31 (86) (71,95)	10 (29) (15,47)	57 (38,76) p-value<0.001

	At the end of Period 3, the percentage of complete responders for the primary endpoint was 86% and 29% in the Isturisa and placebo groups, respectively. The difference in percentage of complete responders between Isturisa and placebo groups was 57%, with 95% two-sided CI of (38, 76). The 95% CI were not presented by individual strata due to the small sample sizes of some of these strata. The key secondary endpoint, complete responder rate after 24 weeks of treatment with Isturisa was achieved by 72/137 patients (52.6%) with 95% two-sided CI of (43.9, 61.1). The lower bound of this 95% CI exceeded 30%, the prespecified threshold for statistical significance and minimum threshold for clinical benefit. At week 48, 91/137 patients (66%) had normal mUFC levels. Variable decreases from baseline for blood pressure, glucose parameters, weight and weight circumference were observed at week 48. However, because the study allowed initiation of anti-hypertensive and anti-diabetic medications and dose increases in patients already receiving such medications and the absence of a control group, the individual contribution of Isturisa or of anti-hypertensive and anti-diabetic medication adjustments cannot be clearly established.(1)
Safety	Isturisa (osilodrostat) has no known FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Isturisa prescribing information. Recordati Rare Disease, Inc. November 2023.
2	Nieman, Lynnette K. Recent Updates on the Diagnosis and Management of Cushing's Syndrome. Endocrinology and Metabolism. 2018 Jun;33:139-146. doi: 10.3803/EnM.2018.33.2.139.
3	Reference no longer used
4	Novartis Pharmaceuticals. A Phase III, Multi-center, Randomized, Double-blind, 48 Week Study With an Initial 12 Week Placebo-controlled Period to Evaluate the Safety and Efficacy of Osilodrostat in Patients With Cushing's Disease. Identification No. NCT02697734. https://clinicaltrials.gov/ct2/show/NCT02697734.
5	Endocrine Society. Cushing's disease. Accessed at: https://www.hormone.org/diseases-and-conditions/cushings-disease
6	Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol December 2021;9 847-75.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Isturisa	Osilodrostat Phosphate Tab 1 MG	1 MG	M ; N ; O ; Y	N		
Isturisa	Osilodrostat Phosphate Tab 5 MG	5 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Isturisa	Osilodrostat Phosphate Tab 1 MG	1 MG	240	Tablets	30	DAYS			
Isturisa	Osilodrostat Phosphate Tab 5 MG	5 MG	360	Tablets	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Isturisa	Osilodrostat Phosphate Tab 1 MG	1 MG	Commercial ; HIM ; ResultsRx
Isturisa	Osilodrostat Phosphate Tab 5 MG	5 MG	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Isturisa	Osilodrostat Phosphate Tab 1 MG	1 MG	Commercial ; HIM ; ResultsRx
Isturisa	Osilodrostat Phosphate Tab 5 MG	5 MG	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

   1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
   2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

   B. The patient has a diagnosis of Cushing's disease AND ALL of the following:
      1. ONE of the following:
         A. The patient had an inadequate response to pituitary surgery **OR**
         B. The patient is NOT a candidate for pituitary surgery **AND**
      2. The patient's disease is persistent or recurrent as evidenced by ONE of the following:
         A. The patient has a mean of three 24-hour urine free cortisol (UFC) greater than 1.3 times the upper limit of normal **OR**

Module	Clinical Criteria for Approval
	B. Morning plasma adrenocorticotropic hormone (ACTH) above the lower limit of normal **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response, to at least ONE of the following conventional agents: 1. Mifepristone 2. Signifor/Signifor LAR (pasireotide) 3. Recorlev (levoketoconazole) 4. Cabergoline 5. Metyrapone 6. Lysodren (mitotane) **OR** B. The patient has an intolerance or hypersensitivity to mifepristone, pasireotide, or levoketoconazole **OR** C. The patient has an FDA labeled contraindication to mifepristone, pasireotide, and levoketoconazole **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to ketoconazole tablets **OR** B. The patient has an intolerance or hypersensitivity to ketoconazole tablets (medical records required) **OR** C. The patient has an FDA labeled contraindication to ketoconazole tablets (medical records required) **AND** 5. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient will NOT be using the requested agent in combination with glucocorticoid replacement therapy **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: Patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with glucocorticoid replacement therapy **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months