Drug Monograph

Drug Name: **Isturisa® (osilodrostat) Tablet**
Drug Class: **Cortisol Synthesis Inhibitor**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Isturisa is available as an oral tablet containing 1 mg, 5 mg or 10 mg of osilodrostat.
Manufacturer:	Distributed by: Recordati Rare Disease, Inc., Lebanon, NJ 08833.
Summary of Findings:	The efficacy of Isturisa for the treatment of Cushing's Disease in adult patients was demonstrated in one placebo-controlled study enrolling 137 patients. The primary efficacy endpoint was to compare the percentage of complete responders at the end of the 8-week randomized withdrawal period. A complete responder was defined as a patient who had mUFC ≤ ULN based on central laboratory results and who had neither discontinued randomized treatment or had any dose increase. The percentage of complete responders was 86% for the Isturisa group vs 29% for the placebo group (95% CI 38, 76; p< 0.001).
Status Recommendation:	☒ Clinical Edit ☐ Open Access ☐ PA Required ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ No PA Required ☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Cushing's disease is caused by a tumor in the pituitary gland secreting adrenocorticotropic hormone which stimulates the over-production of cortisol from the adrenal gland. Cushing's disease affects 10 to 15 million people worldwide, is most common among adults between the ages of 30 to 50, and usually affects females more often than males. Surgery is the first-line option, and has an 80-90% cure rate if a tumor is found. Unfortunately, up to 31 percent of patients fail to achieve remission after surgery. Symptoms of Cushing's disease include weight gain in the trunk, face, and back of neck (buffalo hump), excessive hair growth, bruising easily, muscle weakness, and severe tiredness. Cushing's disease can cause significant health issues including osteoporosis, obesity, anxiety, depression, hypertension and diabetes.

Dosage Form [3]

Isturisa is available as an oral tablet containing 1 mg, 5 mg or 10 mg of osilodrostat.

Manufacturer [3]

Distributed by: Recordati Rare Disease, Inc., Lebanon, NJ 08833.

Indication(s) [3]

Isturisa 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.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Isturisa inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.

Pharmacokinetics:

Absorption	Time to peak: 1 hour
Metabolism	Hepatically metabolized by multiple CYP enzymes (CYP3A4, 2B6, 2D6) and UDP-glucuronosyltransferases to inactive metabolites; no single enzyme contributes to >25% to the total clearance
Excretion	Urine: 90.6% (5.2% as unchanged drug) Feces: 1.58%
Half-life	4 hours

Clinical Trials Experience

STUDY 1 DESIGN	Multicenter study that consisted for 4 study periods (called the Core Period) (n=137): • 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 which provided the data for the primary efficacy endpoint • Period 4- open-label treatment period of 14 to 24 weeks duration
INCLUSION CRITERIA	• Written informed consent must be obtained before any assessment is performed. • Male or female patients aged 18 - 75 years. • Patients must have confirmed Cushing's disease that is persistent or recurrent. • Patients with a history of prior pituitary surgery must be at least 30 days post-surgery to be eligible for inclusion in this study. • Patients that received glucocorticoid replacement therapy post-operatively must have discontinued such therapy for at least one week, or 5 half-lives, whichever is longer, prior to screening. • Patients with de novo Cushing's disease can be included only if they are not considered candidates for surgery. • Patients with a history of pituitary irradiation can be included, provided that at least 2 years (stereotactic radiosurgery) or 3 years (conventional radiation) have elapsed from the time of last radiation treatment to the time of enrollment into this study. • Patients are permitted to washout current drug therapy to meet these entry criteria if they have a known diagnosis of Cushing's disease
EXCLUSION CRITERIA	• Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half lives at the time of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations. • History of hypersensitivity to Isturisa or to drugs of similar chemical classes. • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. • Patients with risk factors for QTc prolongation or Torsade de Pointes. • Pregnant or nursing (lactating) women. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after completion of dosing.

	• Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm (tumor within 2 mm of optic chiasm). • Patients who have a known inherited syndrome as the cause for hormone over secretion. • Patients with Cushing's syndrome due to ectopic ACTH secretion or ACTH-independent (adrenal) Cushing's syndrome. • Patients who have undergone major surgery within 1 month prior to screening. • Hypertensive patients with uncontrolled blood pressure. • Diabetic patients with poorly controlled diabetes. • Patients who are not euthyroid as judged by the investigator. • Patients who have a history of: congestive heart failure, unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, acute MI less than one year prior to study entry, or clinically significant impairment in cardiovascular function. • Patients with moderate to severe renal impairment. • Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with defined elevated ALT/ AST/ Bilirubin. • Patients who have any current or prior medical condition that can interfere with the conduct of the study or the evaluation of its results in the opinion of the investigator or the sponsor's medical monitor. • Patients who have a history of alcohol or drug abuse in the 6 month period prior to study treatment. • Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will be unable to complete the entire study.
TREATMENT REGIMEN	Patients were randomized to receive Isturisa (n=36) or placebo (n=35) for 8 weeks. Patients were stratified at randomization according to dose received at week 24 (≤ 5 mg twice daily vs 5 mg twice daily). The maximum dose was 30 mg twice daily.
RESULTS	The primary efficacy endpoint was to compare the percentage of complete responders at the end of the 8-week randomized withdrawal period 3. A complete responder was defined as a patient who had mUFC ≤ ULN based on central laboratory results and who had neither discontinued randomized treatment or had any dose increase. The percentage of complete responders was 86% for the Isturisa group vs 29% for the placebo group (95% CI 38, 76; p< 0.001).
SAFETY	Discussed in the Adverse Effects section below.

*mUFC= mean urinary free cortisol; ULN= upper limit of normal

Contraindications [3,4]

- None

Warnings and Precautions [3,4]

- 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.

Adverse Effects [3,4]

Most common, ≥ 10%	(n =137) %
Adrenal insufficiency	43.1
Fatigue	38.7
Nausea	37.2
Headache	30.7
Edema	21.2
Nasopharyngitis	19.7
Vomiting	19
Arthralgia	17.5
Back pain	15.3
Rash	15.3
Diarrhea	14.6
Blood corticotrophin increased	13.9
Dizziness	13.9
Abdominal pain	13.1
Hypokalemia	12.4
Myalgia	12.4
Decreased appetite	11.7
Hormone level abnormal	11.7
Hypotension	11.7
Urinary tract infection	11.7
Blood testosterone increased	10.9
Pyrexia	10.9
Anemia	10.2
Cough	10.2
Hypertension	10.2
Influenza	10.2

Drug Interactions [3,4]

- CYP3A4 Inhibitor: Reduce the dose of Isturisa by half with concomitant use of a strong CYP3A4 inhibitor
- CYP3A4 Inducers: An increase of Isturisa dosage may be needed if Isturisa is used concomitantly with strong CYP3A4 and CYP2B6 inducers. A reduction in Isturisa dosage may be needed if strong CYP3A4 and CYP2B6 inducers are discontinued while using Isturisa.

Dosage and Administration [3,4]

- Initiate dosage at 2 mg orally twice daily, with or without food.
- Titrate dosage by 1 to 2 mg twice daily, no more frequently than every 2 weeks based on rate of cortisol changes, individual tolerability and improvement in signs and symptoms.
- Maximum recommended dosage is 30 mg twice daily.
- Hepatic impairment:
    - Child-Pugh B: Recommended starting dose is 1 mg twice daily
    - Child-Pugh C: Recommended starting dose is 1 mg once daily in the evening

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Year
Osilodrostat	Isturisa	Recordati Rare Disease Inc	1 mg to 60 mg/day	$146,000 to $1.04 million

** Wholesale Acquisition Cost

Conclusion

Isturisa 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. The efficacy of Isturisa was demonstrated in one randomized, double-blind, placebo-controlled trial in 137 adults with Cushing's Disease. This trial showed a statistically significant difference in the patients randomized to receive Isturisa in the complete responder rate compared to placebo. The most common adverse drug reactions in patients taking Isturisa (>20%) were adrenal insufficiency, fatigue, nausea, headache, and edema.

Recommendation

The MO HealthNet Division recommends adding this drug to an Isturisa clinical edit.

References

1) Cushing Disease. U.S. National Library of Medicine. https://ghr.nlm.nih.gov. Accessed August 2, 2020.
2) Cushing's Disease News. https://cushingsdiseasenews.com. Accessed August 2, 2020.
3) Product Information: Isturisa® (osilodrostat). Recordati Rare Disease, Inc., Lebanon, NJ 08833.
4) Isturisa: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
5) Phase 3, multi-center, double-blind, randomized withdrawal study of LC1699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LC1699 for the treatment of patients with Cushing's Disease. Clinicaltrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02180217. Accessed August 2, 2020.

Prepared by: Jaci Schowengerdt, PharmD
Date: August 2, 2020

