Isturisa®
(osilodrostat)

QUICK START GUIDE

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Hypocortisolism:** ISTURISA lowers cortisol levels and can lead to hypocortisolism and sometimes life-threatening adrenal insufficiency. Lowering of cortisol can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, and dizziness. Significant lowering of serum cortisol may result in hypotension, abnormal electrolyte levels, and hypoglycemia.

  Hypocortisolism can occur at any time during ISTURISA treatment. Evaluate patients for precipitating causes of hypocortisolism (infection, physical stress, etc). Monitor 24-hr urine free cortisol, serum or plasma cortisol, and patient's signs and symptoms periodically during ISTURISA treatment.

Please see Important Safety Information throughout and click here for full Prescribing Information.

The starting dose

Start your patient on ISTURISA® (osilodrostat) 2 mg twice daily with or without food[1]

Some patient populations may require modifications to their starting dose[1]

Recommended starting dose for patients with hepatic impairment[1]

- Child-Pugh B: 1 mg twice daily
- Child-Pugh C: 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

Recommended starting dose for patients with renal impairment[1]

- No dose adjustment is required[a]

Modifications to the dose of ISTURISA may be necessary in patients concomitantly treated with strong CYP3A4 inhibitors (eg, itraconazole, clarithromycin) or with strong CYP3A4 and CYP2B6 inducers (eg, carbamazepine, rifampin, phenobarbital).[b] Monitor your patients' cortisol levels and signs and symptoms during concomitant treatment with these medications while taking ISTURISA.

CYP3A4 Inhibitors
For patients taking strong CYP3A4 inhibitors, reduce the dose of ISTURISA by half.

CYP3A4 and CYP2B6 Inducers
For patients taking strong CYP3A4 and CYP2B6 inducers, an increase in ISTURISA dosage may be needed. Upon discontinuation of strong CYP3A4 and CYP2B6 inducers, a reduction in ISTURISA dosage may be necessary.

Ask your patients about their current medications and history of hepatic or renal impairment.

What to test for prior to starting ISTURISA[1]

- Test potassium and magnesium levels and correct for hypokalemia and hypomagnesemia
- Obtain baseline electrocardiogram (ECG)

[a]Use caution in interpreting urinary free cortisol (UFC) levels, which may be reduced in patients with moderate to severe renal impairment.[1]
[b]Please see full Prescribing Information for complete dosing recommendations.

Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

- **Hypocortisolism** *(continued)*: Decrease or temporarily discontinue ISTURISA 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. Stop ISTURISA and administer exogenous glucocorticoid replacement therapy if serum or plasma cortisol levels are below target range and patients have symptoms of adrenal insufficiency. After ISTURISA discontinuation, cortisol suppression may persist beyond the 4-hour half-life of ISTURISA. Please see section 5.1 of full Prescribing Information.

  Educate patients on the symptoms associated with hypocortisolism and advise them to contact a healthcare provider if they occur.

Titrating the dose

Titrate ISTURISA® (osilodrostat) in 1- or 2-mg increments twice daily, no more than once every 2 weeks, based on the rate of cortisol changes, individual tolerability, and improvement in signs and symptoms of Cushing's disease[1]

- If your patient tolerates 10 mg twice daily and continues to have elevated 24-hour UFC levels above the upper limit of normal (ULN), you may up-titrate by 5 mg twice daily every 2 weeks
- The maintenance dosage of ISTURISA is individualized and determined by titration based on cortisol levels and patient's signs and symptoms

Multiple dosing options allow you to adjust therapy for each patient's unique needs during titration and maintenance[1]

TABLET SIZES

1 mg[1]		6.1 mm^2
5 mg[1]		7.1 mm^3

Continue monitoring your patients to optimize cortisol levels and help improve Cushing's disease symptoms[1]

- Monitor cortisol levels from at least two 24-hour UFC collections every 1 to 2 weeks until adequate clinical response is maintained
- Repeat ECG within 1 week after treatment initiation, and as clinically indicated thereafter
- Monitor potassium and magnesium levels periodically during treatment with ISTURISA

Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

- **QTc Prolongation:** ISTURISA is associated with a dose-dependent QT interval prolongation which may cause cardiac arrhythmias. Perform an ECG to obtain a baseline QTc interval measurement prior to initiating therapy with ISTURISA and monitor for an effect on the QTc interval thereafter. Correct hypokalemia and/or hypomagnesemia prior to ISTURISA initiation and monitor periodically during treatment with ISTURISA. Use with caution in patients with risk factors for QT prolongation and consider more frequent ECG monitoring. Please see section 5.2 of full Prescribing Information.

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Consider slowly up-titrating your patients[1]

Dose increases are recommended no more frequently than every 2 weeks, but may be titrated more slowly based on patient tolerability[1]

> ***"Reductions in cortisol levels during osilodrostat therapy can lead to hypocortisolism, which may be mitigated by slow dose up-titration."***[4] –Fleseriu et al, *Endocrine Practice*

Consider down-titration, temporary discontinuation, or glucocorticoid replacement therapy if any of the following occur[1]:

- UFC levels fall below the target range
- Cortisol levels rapidly decrease
- Patients report symptoms of hypocortisolism

Counsel your patients to recognize and report any signs and symptoms of hypocortisolism[1]

- Nausea
- Vomiting
- Fatigue
- Abdominal pain
- Loss of appetite
- Dizziness
- Low blood pressure
- Syncope

Significant lowering of serum cortisol may result in hypotension, abnormal electrolyte levels, and hypoglycemia[1]

Hypocortisolism can occur during treatment with ISTURISA® (osilodrostat). Stop treatment and administer glucocorticoid replacement therapy if patients are experiencing signs and symptoms of adrenal insufficiency and have cortisol levels below the target range.[1]

You may restart treatment with ISTURISA if interrupted[1]

Re-initiate ISTURISA at a lower dose when cortisol levels reach the target range and patient symptoms have been resolved.[1]

Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

- **Elevations in Adrenal Hormone Precursors and Androgens:** ISTURISA blocks cortisol synthesis and may increase circulating levels of cortisol and aldosterone precursors and androgens. This may activate mineralocorticoid receptors and cause hypokalemia, edema and hypertension. Hypokalemia should be corrected prior to initiating ISTURISA. Monitor patients treated with ISTURISA for hypokalemia, worsening of hypertension and edema. Inform patients of the symptoms associated with hyperandrogenism and advise them to contact a healthcare provider if they occur. Please see section 5.3 of full Prescribing Information.

Monitoring and dose adjustments, as needed

Help stay in control by monitoring each patient's changes in cortisol

- The maintenance dosage of ISTURISA® (osilodrostat) is individualized and determined by titration based on cortisol levels and each patient's signs and symptoms[1]
- Although the maximum maintenance dosage of ISTURISA is 30 mg twice daily, the maintenance dosage in clinical trials varied between 2 mg and 7 mg twice daily[1,4]

Periodically test once maintenance dosage is achieved[1]

- Monitor cortisol levels at least every 1 to 2 months or as indicated
- Monitor magnesium and potassium levels
- Repeat ECG as clinically indicated

Regular monitoring allows you to make more informed titration decisions[1]

Important Safety Information *(continued)*

Adverse Reactions

- Most common adverse reactions (incidence >20%) are adrenal insufficiency, fatigue, nausea, headache, and edema.
- **To report SUSPECTED ADVERSE REACTIONS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

Please see Important Safety Information throughout and click here for full Prescribing Information.

Isturisa® (osilodrostat)

R.A.R.E.®
Recordati Access, Resources, and Engagement

A collaboration of support and services

ISTURISA® (osilodrostat) is available exclusively through the R.A.R.E.® patient support program

- Designed to ensure your patients taking ISTURISA receive dedicated, multipoint services and support every way

ACCESS AND FINANCIAL ASSISTANCE

DISPENSING AND DELIVERY

EDUCATION AND ADHERENCE

RRD OFFERS A **$20 CO-PAY** FOR QUALIFIED PATIENTS WITH COMMERCIAL INSURANCE

Your one-stop source to starting a new patient, plus access to a full range of Recordati Rare Diseases tools and resources.

TO GET YOUR PATIENT STARTED:

STEP 1:
FILL OUT A PATIENT PRESCRIPTION FORM

- Visit **RareResources.com** or scan here to download patient prescription forms

STEP 2:
SUBMIT THE FORM

- **Fax** the fully completed Patient Prescription Form to Anovo Specialty Rx at **1-855-813-2039**
  – NCPDP #: 4445640

OR

- **Electronically submit** the form in your EMR system
  – When ordering, choose **Anovo#5**
  – NCPDP #: 4445640

Contact the **R.A.R.E.** Patient Support Program for assistance
Monday–Friday between 8:00 AM and 8:00 PM ET
Phone: **1-888-855-RARE (7273)** Fax: **1-855-813-2039**
A clinical pharmacist is always available.

R.A.R.E.®
Recordati Access, Resources, and Engagement

R.A.R.E.® support for you and your patient

The R.A.R.E. Program will work with you and your patient to validate insurance information and navigate financial and access assistance

1. Once the completed referral form is received, the R.A.R.E. support team will:
   - Investigate your patient's insurance benefits
   - Help coordinate co-pay card assistance
   - Help identify other financial assistance opportunities, if necessary

2. A member of the R.A.R.E. team will fax your office the appropriate prior authorization form or provide a CoverMyMeds Key once the benefit investigation is complete
   - Please reach out to the R.A.R.E. team (**1-888-855-7273**) if you have questions regarding required documentation or laboratory testing for prior authorization

3. Once benefits have been established, a pharmacist will contact your patient to arrange for overnight delivery of ISTURISA® (osilodrostat)

After enrollment, our R.A.R.E. outreach team assists your patients proactively, and on demand, throughout their ISTURISA journey

- Regular calls to the patient, which may assist the provider in assessing their adherence and experience
- You will be alerted if any issues arise that require your attention or need patient follow-up
- Pharmacy support is available 24/7

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Important Safety Information *(continued)*

Drug Interactions

- **CYP3A4 Inhibitor:** Reduce the dose of ISTURISA by half with concomitant use of a strong CYP3A4 inhibitor.
- **CYP3A4 and CYP2B6 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.

Use in Specific Populations

- **Lactation:** Breastfeeding is not recommended during treatment with ISTURISA and for at least one week after treatment.

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R.A.R.E.®

Recordati Access, Resources, and Engagement

A collaboration of support and services

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A representative from R.A.R.E.® will investigate patient insurance benefits, discuss the co-pay program and other financial assistance, and support any prior authorization requirements.

Once benefits have been established, **a pharmacist will contact your patient** to arrange for overnight delivery of ISTURISA.

Contact the R.A.R.E. Patient Support Program for assistance

Monday-Friday between 8:00 AM and 8:00 PM ET

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A clinical pharmacist is always available.

References

References: 1. Isturisa. Package insert. Recordati Rare Diseases, Inc; 2023. **2.** Data on file 1. Recordati Rare Diseases Inc; 2020. **3.** Data on file 2. Recordati Rare Diseases Inc; 2020. **4.** Fleseriu M, Auchus RJ, Snyder PJ, et al. Effect of dosing and titration of osilodrostat on efficacy and safety in patients with Cushing's disease (CD): results from two phase III trials (LINC3 and LINC4). *Endocr Pract*. 2021;27(suppl 6):S112. Abstract #999926. doi:10.1016/j.eprac.2021.04.707

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RECORDATI RARE DISEASES

Focused on the Few®