

# Helpful Answers to FREQUENTLY ASKED QUESTIONS

## **INDICATIONS AND USAGE**

ISTURISA<sup>®</sup> (osilodrostat) is indicated for the treatment of endogenous hypercortisolemia in adults with Cushing's syndrome for whom surgery is not an option or has not been curative.

## **IMPORTANT SAFETY INFORMATION**

**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.

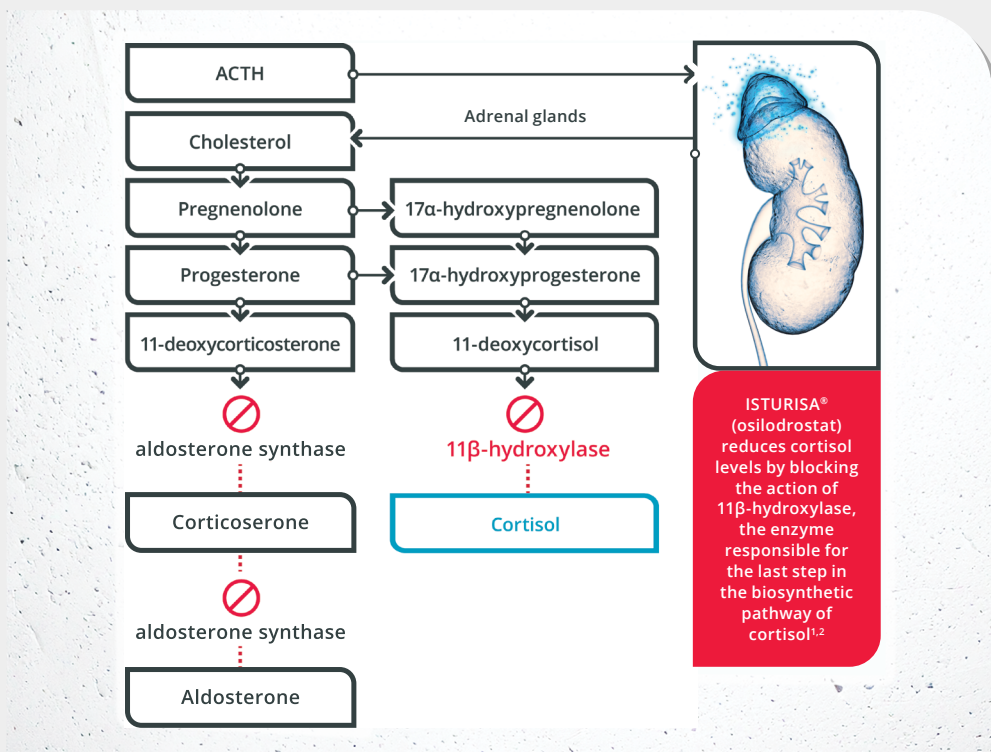
Hypocortisolism can occur at any time during ISTURISA treatment. Evaluate patients for precipitating causes of hypocortisolism (infection, physical stress, etc.). Monitor 24-hr urine free cortisol, serum or plasma cortisol, and patient's signs and symptoms periodically during ISTURISA treatment.

**Please see Important Safety Information throughout and accompanying full Prescribing Information.**

# ISTURISA is a targeted cortisol synthesis inhibitor<sup>1,2</sup>

## How does ISTURISA work?

ISTURISA® (osilodrostat) is the first FDA-approved therapy that blocks the enzyme 11 $\beta$ -hydroxylase to help normalize cortisol in patients with Cushing's syndrome (CS).<sup>1,3,4</sup>



## What is the effect of ISTURISA on adrenocorticotrophic hormone (ACTH) levels?

A dose-dependent increase was observed in ACTH levels in patients with CS.<sup>1</sup>

## Does ISTURISA affect aldosterone levels?

Due to the mechanism of action, treatment with ISTURISA may result in increased circulating levels of cortisol and aldosterone precursors (11-deoxycortisol and 11-deoxycorticosterone) and androgens. Elevated 11-deoxycorticosterone levels may activate mineralocorticoid receptors and cause hypokalemia, edema, and hypertension (see the full Prescribing Information Section 6 Adverse Reactions). Hypokalemia should be corrected prior to initiating ISTURISA. Patients treated with ISTURISA should be monitored for hypokalemia, worsening of hypertension and edema (see the full Prescribing Information Section 5.3).<sup>1</sup>

## How is ISTURISA different from other treatment options for CS?

There are currently no head-to-head studies comparing ISTURISA to other approved treatment options for CS.<sup>5</sup> However, unlike cortisol receptor blockers, ISTURISA lets you objectively monitor each patient's individual changes in cortisol.<sup>1,6</sup>

*In clinical trials,*

## A variety of patients with CS were studied

### Who may be an appropriate patient for treatment with ISTURISA® (osilodrostat)?

ISTURISA is indicated for the treatment of endogenous hypercortisolemia in adult patients with CS for whom surgery is not an option or has not been curative.<sup>1</sup>

Clinical studies included patients with one or more:

- previous medical therapy<sup>7,8</sup>
- previous pituitary irradiation<sup>7,8</sup>
- pituitary surgery<sup>7,8</sup>
- obesity<sup>9,10</sup>
- hypertension<sup>9,10</sup>
- diabetes<sup>9,10</sup>
- osteoporosis<sup>9,10</sup>

### Can patients with renal or hepatic impairment take ISTURISA?

Yes. In patients with renal impairment, no dose adjustments are required. In patients with moderate to severe renal impairment, urine free cortisol (UFC) levels should be interpreted with caution due to reduced UFC excretion. Dose adjustments are not required in patients with mild hepatic impairment (Child-Pugh A) but are required for patients with moderately impaired hepatic function (Child-Pugh B) and severe hepatic impairment (Child-Pugh C).<sup>1,a</sup>

<sup>a</sup>The recommended starting dose for patients with moderate hepatic impairment (Child-Pugh B) is 1 mg twice daily; for patients with severe hepatic impairment (Child-Pugh C), the recommended starting dose is 1 mg once daily in the evening.<sup>1</sup> More frequent monitoring of adrenal function may be required during dose titration in all patients with hepatic impairment [see Clinical Pharmacology (12.3) in the Prescribing Information].

### What's the onset time and half-life for ISTURISA?

ISTURISA is administered orally with or without food twice daily and has a half-life of  $\approx 4$  hours. ISTURISA reaches its max concentration ( $T_{max}$ ) within approximately 1 hour. After ISTURISA discontinuation, cortisol suppression may persist beyond the 4-hour half-life of ISTURISA. Exposure ( $AUC_{inf}$  and  $C_{max}$ ) is not affected in patients with renal impairment but  $AUC_{inf}$  may be increased in patients with moderate to severe hepatic impairment.<sup>1</sup>

### Where can I find information on the clinical trials for ISTURISA?

The clinical trial program for osilodrostat encompassed two phase 3 studies, LINC 3 and LINC 4, designed to assess the safety and efficacy of osilodrostat in patients with Cushing's Disease.<sup>7,8</sup> The LINC 3 study assessed the proportion of participants achieving mean UFC (mUFC)  $\leq$  ULN at the end of the 8-week randomized withdrawal period, without any up-titration during this period.<sup>7</sup> The LINC 4 study evaluated the proportion of participants achieving mUFC  $\leq$  ULN at the end of a 12-week, double-blind, placebo-controlled period.<sup>8</sup> The LINC 4 study design allowed for a slower titration (approximately every 3 weeks) than LINC 3 (every 2 weeks).<sup>7,8</sup>

To find more information about these 2 trials, please visit [ISTURISA.com/hcp/clinical-studies](https://www.isturisa.com/hcp/clinical-studies) or scan here.



### Important Safety Information (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 interruption or discontinuation, cortisol suppression may persist beyond the 4-hour half-life of ISTURISA.

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

# Safety profile

## Does ISTURISA® (osilodrostat) affect tumor growth?

A similar percentage of patients experienced a  $\geq 20\%$  increase or decrease in tumor volume at week 48 in LINC 3. There was no correlation between tumor volume increase and increase in ACTH or with the total and last dose of ISTURISA used during the studies.<sup>1,7,8,10</sup>

## How long does it take for cortisol levels to normalize in CD patients treated with ISTURISA?

In LINC 3 and LINC 4, the median time to first complete response (mUFC  $\leq$  ULN) was 41 days and 35 days, respectively.<sup>7,8</sup> The ULN for UFC was defined as 138 nmol/24 h or 50  $\mu\text{g}/24\text{ h}$ .<sup>7,8</sup>

## What is the safety profile of ISTURISA?

### The most common adverse reactions with ISTURISA in the LINC 3 study were (>15% frequency)<sup>1</sup>:

- |                                              |                              |                             |
|----------------------------------------------|------------------------------|-----------------------------|
| • Adrenal insufficiency <sup>a</sup> (43.1%) | • Edema <sup>d</sup> (21.2%) | • Back pain (15.3%)         |
| • Fatigue <sup>b</sup> (38.7%)               | • Nasopharyngitis (19.7%)    | • Rash <sup>e</sup> (15.3%) |
| • Nausea (37.2%)                             | • Vomiting (19.0%)           |                             |
| • Headache <sup>c</sup> (30.7%)              | • Arthralgia (17.5%)         |                             |

### The most common adverse reactions in the LINC 4 study were (>20% frequency)<sup>8</sup>:

- |                              |                                        |                                             |
|------------------------------|----------------------------------------|---------------------------------------------|
| • Arthralgia (45.2%)         | • Myalgia (26.0%)                      | • Diarrhea (23.3%)                          |
| • Decreased appetite (45.2%) | • Dizziness (26.0%)                    | • Hypertension (21.9%)                      |
| • Fatigue (38.4%)            | • Adrenal insufficiency (24.7%)        | • Asthenia (20.5%)                          |
| • Nausea (37.0%)             | • Increased blood testosterone (24.7%) | • Upper respiratory tract infection (20.5%) |
| • Headache (32.9%)           |                                        |                                             |

**Description of Select Adverse Reactions from the Core 48-week Period of Study 1 (LINC 3):** Hypocortisolism was reported at a rate of 31% up to 12 weeks, and 18% from Weeks 12 to 26. The majority of cases were manageable by reducing the dose of ISTURISA and/or adding low-dose, short-term glucocorticoid therapy.<sup>1</sup>

**Description of Selected Adverse Reactions from the 12-week Placebo-Controlled Period of Study 2 (LINC 4):** Hypocortisolism was reported at a rate of 15% in ISTURISA arm and no subjects in placebo arm. The majority of cases were manageable by interrupting/reducing the dose of ISTURISA and/or adding low-dose, short-term glucocorticoid therapy.<sup>1</sup>

<sup>a</sup>Adrenal insufficiency includes glucocorticoid deficiency, adrenocortical insufficiency acute, steroid withdrawal syndrome, cortisol free urine decreased, cortisol decreased. One-third of the subjects with this event had low cortisol levels indicative of adrenal insufficiency. The majority of subjects had normal cortisol levels suggesting a cortisol withdrawal syndrome.

<sup>b</sup>Fatigue includes lethargy, asthenia.

<sup>c</sup>Headache includes head discomfort.

<sup>d</sup>Edema includes edema peripheral, generalized edema, localized edema.

<sup>e</sup>Rash includes rash erythematous, rash generalized, rash maculopapular, rash papular.

# Dosing and patient monitoring

## What are the available doses of ISTURISA® (osilodrostat)?

ISTURISA is available in 2 tablet sizes for flexible dosing options.<sup>1</sup>

The starting dose of ISTURISA is 2 mg twice daily. The maximum recommended dosage of ISTURISA is 30 mg twice daily.<sup>1</sup>



### TABLET SIZES:

1 mg<sup>1</sup>  6.1 mm<sup>12</sup>

5 mg<sup>1</sup>  7.1 mm<sup>13</sup>

## What laboratory tests should be evaluated for patients receiving ISTURISA?

### Before starting ISTURISA<sup>1</sup>:

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

### During titration<sup>1</sup>:

- 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

### Once maintenance dosage is achieved<sup>1</sup>:

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

Hypocortisolism can occur at any time during ISTURISA treatment. Monitor 24-hour urinary free cortisol, serum or plasma cortisol, and patient's signs and symptoms periodically.<sup>1</sup>

## Should I evaluate my patients for QTc prolongation?

Five patients (4%) in the LINC 3 study experienced QT prolongation. Before starting ISTURISA, obtain a baseline ECG to determine a baseline QTc interval measurement; repeat in 1 week and as clinically indicated thereafter. Consider more frequent monitoring in patients with risk factors for QT prolongation or who are taking concomitant medications known to prolong the QT interval.<sup>1</sup>

## Important Safety Information (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.

# Getting your patient started

## What are the starting dose and titration recommendations for ISTURISA® (osilodrostat)?

Start your patient on 2 mg twice daily<sup>a</sup> with or without food.<sup>1</sup> Titrate ISTURISA 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 syndrome.<sup>1</sup>

Slower dose titration may reduce the adverse effects of hypocortisolism.<sup>8</sup> To learn more about ISTURISA dosing and titration, please see the full Prescribing Information (Section 2.2 Recommended Dosage, Titration, and Monitoring).

## Do I need to monitor cortisol with ISTURISA?

During the titration phase, monitor cortisol levels from at least two 24-hour UFC collections every 1 to 2 weeks until normal cortisol levels are achieved and maintained. Once your patient has reached their maintenance dosage, monitor cortisol levels at least every 1 to 2 months or as clinically indicated.<sup>1</sup>

## How do I start a patient on ISTURISA?

To get your patient started, fill out a Patient Prescription Form by scanning here or going to [ISTURISA.com/hcp/resources-support/](https://www.isturisa.com/hcp/resources-support/).



Once you've filled out and faxed the Patient Prescription Form to **1-855-813-2039** or electronically submitted it in your EMR system, a representative from Recordati Access, Resources, and Engagement (R.A.R.E.®) will coordinate with you, your staff, and your patient to facilitate patient access.

## Is there a co-pay program or financial assistance to help patients pay for ISTURISA?

The R.A.R.E. program will work with you and your patient throughout the access process. Once the completed prescription form is received, the R.A.R.E. team will investigate your patient's insurance benefits, help coordinate co-pay card assistance,<sup>b</sup> and help identify other financial assistance opportunities, as needed.

<sup>a</sup>The recommended starting dose for patients with moderate hepatic impairment (Child-Pugh B) is 1 mg twice daily; for patients with severe hepatic impairment (Child-Pugh C), the recommended starting dose is 1 mg once daily in the evening.<sup>1</sup>

<sup>b</sup>For commercially eligible patients.

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

# IMPORTANT SAFETY INFORMATION

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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.

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 interruption or discontinuation, cortisol suppression may persist beyond the 4-hour half-life of ISTURISA.

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

**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.

**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.

**The most common adverse reactions** (incidence >20%) are adrenal insufficiency, fatigue, nausea, headache, edema, decreased appetite, arthralgia, myalgia, and diarrhea.

**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](http://www.fda.gov/medwatch).**

## 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.

**Dosage Interruptions and Modifications:** If treatment is interrupted, re-initiate ISTURISA at a lower dose when cortisol levels are within target ranges and patient symptoms have been resolved.

ISTURISA® (osilodrostat) tablets, for oral use, is available as 1 mg and 5 mg tablets.



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.*

Visit [RareResources.com](https://RareResources.com) for your one-stop source to  
starting a new patient on ISTURISA plus access to a full  
range of Recordati Rare Diseases tools and resources.

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care and advice of your health care providers.



Scan here to find the answers to more questions  
about ISTURISA

**References:** 1. Isturisa. Package insert. Recordati Rare Diseases Inc; 2025. 2. Bertagna X, Pivonello R, Fleseriu M, et al. LCI699, a potent 11 $\beta$ -hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. *J Clin Endocrinol Metab.* 2014;99(4):1375-1383. doi:10.1210/jc.2013-2117 3. FDA approves new treatment for adults with Cushing's disease. News release. US Food and Drug Administration. March 6, 2020. Accessed February 1, 2024. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-cushings-disease> 4. Perosevic M, Tritos NA. Clinical utility of osilodrostat in Cushing's disease: review of currently available literature. *Drug Des Devel Ther.* 2023;17:1303-1312. doi:10.2147/DDDT.S315359 5. Clinical Trials.gov. Clinicaltrials.gov database search engine. Search results for "osilodrostat clinical trials." Accessed February 1, 2024. <https://classic.clinicaltrials.gov/ct2/results?cond=osilodrostat&term=&cntry=&state=&city=&dist=> 6. Korlym. Package insert. Corcept Therapeutics Inc; 2019. 7. Pivonello R, Fleseriu M, Newell-Price J, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. *Lancet Diabetes Endocrinol.* 2020;8(9):748-761. doi:10.1016/S2213-8587(20)30240-0 8. Gadelha M, Bex M, Feelders RA, et al. Randomized trial of osilodrostat for the treatment of Cushing disease. *J Clin Endocrinol Metab.* 2022;107(7):e2882-e2895. doi:10.1210/clinem/dgac178 9. Fleseriu M, Newell-Price J, Pivonello R, et al. Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension. *Eur J Endocrinol.* 2022;187(4):531-541. doi:10.1530/EJE-22-0317 10. Gadelha M, Snyder PJ, Witek P, et al. Long-term efficacy and safety of osilodrostat in patients with Cushing's disease: results from the LINC 4 study extension. *Front Endocrinol (Lausanne).* 2023;14:1236465. doi:10.3389/fendo.2023.1236465 11. 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 12. Data on file 1. Recordati Rare Diseases Inc; 2020. 13. Data on file 2. Recordati Rare Diseases Inc; 2020.

**Please see Important Safety Information throughout and accompanying full Prescribing Information.**



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