PDL DRUG REVIEW

Proprietary Name: Isturisa®
Common Name: osilodrostat
PDL Category: Cushing's Disease Treatments

Comparable Products	Preferred Drug List Status
Signifor	Non-Preferred

Summary

Pharmacology/Usage: Osilodrostat, the active ingredient of 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.

Indication: For the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

There is no pregnancy category for this medication; however, the risk summary indicates there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with active Cushing's Syndrome during pregnancy. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Tablets: 1mg, 5mg, 10mg

Recommended Dosage: Correct hypokalemia and hypomagnesemia prior to starting Isturisa®. Obtain baseline electrocardiogram (ECG), and repeat ECG within one week after treatment initiation, and as clinically indicated thereafter.

Start at 2mg PO BID, with or without food. Initially, titrate the dosage by 1 to 2mg BID, no more frequently than every 2 weeks based on the rate of cortisol changes, individual tolerability and improvement in signs and symptoms of Cushing's disease. If a patient tolerates Isturisa® 10mg BID and continues to have elevated 24-hour urine free cortisol (UFC) levels above upper normal limit, the dosage can be titrated further by 5mg BID every 2 weeks. Monitor cortisol levels from at least two 24-hour urine free cortisol collections every 1-2 weeks until adequate clinical response is maintained. The maintenance dosage of Isturisa® is individualized and determined by titration based on cortisol levels and patient's signs and symptoms.

The maintenance dose varied between 2mg and 7mg BID in clinical trials, with the maximum recommended maintenance dose being 30mg BID. Once the maintenance dosage is achieved, monitor cortisol levels at least every 1-2 months or as indicated.

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. If necessary, glucocorticoid

replacement therapy should be started. 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. If treatment is interrupted, re-start Isturisa® at a lower dose when cortisol levels are within target ranges and patient symptoms have been resolved.

Dose adjustments are not required with renal impairment. Use caution in interpreting urine free cortisol levels in patients with moderate to severe renal impairment, due to reduced urine free cortisol excretion. Dose adjustments are not required with mild hepatic impairment. With moderate hepatic impairment, the recommended starting dose is 1mg BID. With severe hepatic impairment, the recommended starting dose is 1mg QPM. More frequent monitoring of adrenal function may be required during dose titration in all patients with hepatic impairment.

Drug Interactions: Concomitant use of Isturisa® with a strong CYP3A4 inhibitor (e.g. itraconazole, clarithromycin) may cause an increase in osilodrostat concentration and may increase the risk of Isturisa®-related adverse events. Reduce the dose of Isturisa® by half with concomitant use of a strong CYP3A4 inhibitor.

Concomitant use of Isturisa® with strong CYP3A4 and/or CYP2B6 inducers (e.g. carbamazepine, rifampin, phenobarbital) may cause a decrease in osilodrostat concentration and may reduce the efficacy of Isturisa®. During concomitant use of Isturisa® with strong CYP3A4 and CYP2B6 inducers, monitor cortisol concentration and patient's signs and symptoms. An increase in Isturisa® dosage may be needed. Upon discontinuation of strong CYP3A4 and CYP2B6 inducers during Isturisa® treatment, monitor cortisol concentration and patient's signs and symptoms. A reduction in Isturisa® dosage may be needed.

Isturisa® should be used with caution when co-administered with CYP1A2 and CYP2C19 substrates with a narrow therapeutic index, such as theophylline, tizanidine, and S-mephenytoin.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Isturisa®). There was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included 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%), hirsutism (9.5%), acne (8.8%), dyspepsia (8%), insomnia (8%), anxiety (7.3%), depression (7.3%), gastroenteritis (7.3%), malaise (6.6%), tachycardia (6.6%), alopecia (5.8%), transaminases increased (4.4%), electrocardiogram QT prolongation (3.6%), and syncope (1.5%).

Isturisa® lowers cortisol levels and can lead to low cortisol levels and sometimes life-threatening adrenal insufficiency. This can occur at any time during Isturisa® treatment. Assess patients for precipitating causes of hypocortisolism. Monitor 24-hour 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 adrenal insufficiency.

Isturisa® is associated with a dose-dependent QT interval prolongation (maximum mean estimated QTcF increase of up to 5.3ms at 30mg), which may cause cardiac arrhythmias. Perform an ECG to obtain a baseline QTc interval measurement prior to starting therapy with Isturisa® and monitor for an effect on the QTc interval thereafter. Correct hypokalemia and/or hypomagnesemia prior to starting Isturisa® and monitor periodically during treatment. Correct electrolyte abnormalities if indicated. Consider temporary discontinuation of Isturisa® in the case of an increase in QTc interval >480ms. Use caution in patients with risk factors for QT prolongation (such as congenital long QT syndrome, congestive heart failure, bradyarrhythmia, uncorrected electrolyte abnormalities, and concomitant medications known to prolong the QT interval) and consider more frequent ECG monitoring.

Isturisa® blocks cortisol synthesis and may increase circulating levels of cortisol and aldosterone precursors and androgens. Elevation of these precursor levels may activate mineralocorticoid receptors and cause hypokalemia, edema, and hypertension. Hypokalemia should be corrected prior to starting treatment. Monitor patients treated with Isturisa® for hypokalemia, worsening of hypertension, and edema. Accumulation of androgens may lead to hirsutism, hypertrichosis, and acne (in females).

Contraindications: There are no contraindications listed with this product.

Manufacturer: Recordati Rare Disease, Inc

Analysis: The safety and efficacy of Isturisa® were assessed in a 48-week multicenter study that consisted of 4 study periods, including:

- 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

The study included Cushing's disease patients with persistent or recurrent disease despite pituitary surgery or de novo patients for whom surgery was not indicated or who had refused surgery. The mean age of included patients was 41 years, while 77% were female, 65% were Caucasian, and 96% had received previous treatments for Cushing's disease prior to entering the study, of which 88% had undergone surgery. The mean urine free cortisol (mUFC) at baseline was 1006 nmol/24 hour, which corresponds to about 7 times the upper limit of normal (ULN).

During *Period 1*, 137 patients received a starting dose of 2mg Isturisa® BID that could be titrated up to a maximum of 30m BID at no greater than 2-week intervals to achieve a mUFC within the normal range. There were 130 patients who entered *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 ≤ ULN at week 24 (end of Period 2) were to be considered responders and eligible to enter Period 3. Patients whose mUFC became elevated during Period 2 could have their dose increased further, if tolerated, up to 30mg BID. 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 mUFC at week 12 and were followed for long-term safety and response to treatment.

At the start of *Period 3*, 71 patients were considered responders and were randomized to continue receiving Isturisa® or to switch to placebo for 8 weeks. Patients were to remain on their assigned treatment and dose throughout Period 3 if mUFC were within the normal range. Dose increases were not permitted during Period 3, but blinded dose reduction or temporary discontinuation for safety or tolerability reasons were allowed. Patients with mUFC increase >1.5 X ULN or who required a dose increase were considered non-responders and discontinued from Period 3 but allowed to received open-label treatment during Period 4. To conclude, *Period 4* 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®, per the Investigator, had an option to enter an extension period.

The primary efficacy endpoint 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 ≤ 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 ≤ 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.

Results suggested that 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%. Results can be seen in the table below, which was adapted from the prescribing information.

Trial 1	Isturisa® (N=36)	Placebo (N=34)	Complete responder rate Difference
Complete responder rate at end of 8-week randomized withdrawal period (wk 34)	31 (86%)	10 (29%)	57% (p<0.001)

The key secondary outcome, complete responder rate after 24 weeks of treatment with Isturisa®, was achieved by 72/137 patients (52.6%). At week 48, 91/137 (66%) had normal mUFC levels.

Variable decreases from baseline for blood pressure, glucose parameters, weight and weight circumference were seen 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.

Place in Therapy: Isturisa® 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. In a clinical trial, the percentage of complete responders for the primary endpoint was significantly higher with Isturisa® as compared with placebo.

There is no evidence at this time to support that Isturisa® is safer or more effective than the currently available medications. It is therefore recommended that Isturisa® remain non-preferred and require prior authorization in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Isturisa [package insert]. Lebanon, NJ: Recordati Rare Disease, Inc; 2020.