RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Isturisa®
Generic Name	osilodrostat
Drug Manufacturer	Recordati Rare Disease, Inc.

New Drug Approval

FDA Approval Date: March 06, 2020

Review Designation: Standard, Orphan

Review type: New Drug Application 212801

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Cushing's disease is caused by a pituitary tumor that releases too much of a hormone called adrenocorticotropin, which stimulates the adrenal gland to produce an excessive amount of cortisol.

Cushing's syndrome is a rare disorder with an annual incidence of 2–3/million of which benign adrenal adenomas account for 0.6/million. The female:male ratio is 3:1. Preliminary data indicate a high proportion of subclinical Cushing's syndrome in certain risk populations such as patients with type 2 diabetes or osteoporosis. The clinical implications of these observations are presently unclear. Surgery remains first line treatment for overt disease and initial cure or remission is obtained in 65–85% of patients with Cushing's disease. Late recurrences, however, occur in up to 20% and the risk does not seem to plateau even after 20 years of follow-up. A 2- to 3-fold increase in mortality is observed in most studies, and this excess mortality seems confined to patients in whom initial cure was not obtained. Cushing's syndrome continues to pose diagnostic and therapeutic challenges and life-long follow-up is mandatory.

Efficacy

Isturisa's safety and effectiveness for treating Cushing's disease among adults was evaluated in a study of 137 adult patients (about three-quarters women) with a mean age of 41 years. The majority of patients either had undergone pituitary surgery that did not cure Cushing's disease or were not surgical candidates. In the 24-week, single-arm, open-label period, all patients received a starting dose of 2 milligrams (mg) of Isturisa twice a day that could be increased every two weeks up to 30 mg twice a day. At the end of this 24-week period, about half of patients had cortisol levels within normal limits. After this point, 71 patients who did not need further dose increases and tolerated the drug for the last 12 weeks entered an eight-week, double-blind, randomized withdrawal study where they either received Isturisa or a placebo (inactive treatment). At the end of this withdrawal period, 86% of patients receiving Isturisa maintained cortisol levels within normal limits compared to 30% of patients taking the placebo.

Safety

ADVERSE EVENTS

Most common adverse reactions (incidence > 20%) are adrenal insufficiency, fatigue, nausea, headache, edema.

WARNINGS & PRECAUTIONS

- 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.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Osilodrostat is a cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland. In a Chinese hamster lung cell line V79-4 that overexpresses human CYP11B1, adrenodoxin and adrenodoxin reductase, osilodrostat inhibited the activity of human CYP11B1 dose-dependently with IC50 values of 2.5 ± 0.1 nM (n = 4).

Dose & Administration

ADULTS

Correct hypokalemia and hypomagnesemia prior to initiating therapy. Obtain baseline ECG; repeat ECG within 1 week after treatment initiation, and as clinically indicated thereafter.

Oral: Initial: 2 mg twice daily. Titrate by 1 to 2 mg twice daily no more frequently than every 2 weeks according to rate of cortisol changes, tolerability, and clinical response. If patient tolerates a dosage of 10 mg twice daily but cortisol target is not achieved, dosage may be increased by 5 mg twice daily every 2 weeks; typical maintenance dosage: 2 to 7 mg twice daily (maximum: 30 mg twice daily).

PEDIATRICS

The safety and effectiveness of ISTURISA in pediatric patients have not been established.

GERIATRICS

Of the 167 patients in clinical trials with ISTURISA, 10 (6%) were 65 years and older. There were no patients above 75 years of age. Based on the available data on the use of ISTURISA in patients older than 65 years, no dosage adjustment is required.

RENAL IMPAIRMENT

No dosage adjustment of ISTURISA in patients with impaired renal function is required. In patients with moderate to severe renal impairment, UFC levels should be interpreted with caution due to reduced UFC excretion.

HEPATIC IMPAIRMENT

Dosage adjustment is not required in patients with mild hepatic impairment (Child-Pugh A) but is required for patients with moderately impaired hepatic function (Child-Pugh B) and for patients with severe hepatic impairment (Child-Pugh C). More frequent monitoring of adrenal function may be required during dose titration in all patients with hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 1 mg, 5 mg, and 10 mg