NEW DRUG APPROVAL

Brand Name	Recorlev®
Generic Name	levoketoconazole
Drug Manufacturer	Xeris Pharmaceuticals

New Drug Approval

FDA approval date: December 30, 2021

Review designation: Standard; Orphan

Type of review: Type 2 - New Active Ingredient, New Drug Application (NDA): 214133

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Cushing's syndrome (CS) refers to a constellation of symptoms that occur from chronic exposure to excess amounts of glucocorticoids (exogenous or endogenous). CS can result from many etiologies, which are categorized based on adrenocorticotropic hormone (ACTH) dependency. CS can also be iatrogenic, caused by long-term use of exogenous glucocorticoids. The endogenous causes of CS include:

- **ACTH-dependent**
  - Pituitary adenoma (Cushing's disease)
  - Ectopic secretion by non-pituitary tumor
- **ACTH-independent**
  - Adrenocortical adenoma or carcinoma
  - Nodular adrenal hyperplasia

Endogenous Cushing's syndrome is rare, with an incidence of 0.7–2.4 per million population per year. although estimates vary significantly

Efficacy

FDA approved Xeris Biopharma's Recorlev® (levoketoconazole) for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative. Levoketoconazole is the pure 2S,4R enantiomer of ketoconazole. Recorlev® is initiated at a dosage of 150 mg twice daily, with or without food and is titrated by 150 mg/day increments, no more frequently than every 2–3 weeks to a maximum recommended dose of 600 mg twice daily.

The FDA's approval of Recorlev® was based on two Phase 3 studies, summarized in Table 1.

Table 1. Study Design Summary		
	Study 1: LOGICS (NCT03277690)	**Study 2: SONICS (NCT01838551)**
Structure	Open-label dose titration and maintenance phase (up to 19 weeks) followed by an 8-week double-blind, placebo-controlled, randomized withdrawal phase	Open-label, single-arm, multicenter study consisting of dose titration, maintenance, and extended evaluation phases, which totaled an estimated treatment duration of 73 weeks
Study Population	• Patients with persistent or recurrent disease despite surgery, previously medically treated patients, and previously untreated patients • Patients with pituitary or adrenal carcinoma were excluded	

	• Etiology of CS:
	  ○ CD: 83%
	  ○ Adrenal CS: 10%
	  ○ Ectopic ACTH secretion: 2%
	  ○ Unknown: 5%
	• Mean age: 45 years
	• 76% female
		• Etiology of CS:
		  ○ CD: 85%
		  ○ Adrenal CS: 9%
		  ○ Ectopic ACTH secretion: 1%
		  ○ Unknown: 5%
		• Mean age: 44 years
		• 82% female

Interventions	• All patients started on Recorlev in dose titration and maintenance phase (14–19 weeks) • 39 patients from initial phase entered randomized withdrawal phase, and were randomized 1:1 to continue Recorlev or receive placebo for 2 months or until early rescue was necessary	• Three treatment phases: 1. Dose titration (2–21 weeks); patients entered maintenance phase once a therapeutic dose was achieved (n = 94) 2. 6-month maintenance phase 3. Extended evaluation for another 6 months
Endpoints	• Primary endpoint: Number of patients with loss of therapeutic response to Recorlev upon withdrawing to placebo compared with those who continued on treatment • Key secondary endpoint: Proportion of patients with a mUFC normalization at the end of the randomized withdrawal phase	• Primary endpoint: Proportion of patients with normalization of mUFC at the end of the 6- month maintenance phase, **without an increase in dose at any time during maintenance (in the intention-to-treat population)** • Key secondary endpoint: Proportion of patients with a mUFC normalization
Results	• 11/21 (52.4%) patients in the Recorlev group vs. 1/18 (5.6%) in the placebo group met the key secondary endpoint • The treatment difference (CI) was 46.8% (16.5%, 70.2%).	• 29/94 patients (30.9%) patients met the primary endpoint • 95% CI: 21.7%, 41.2%

Abbreviations: ACTH, adrenocorticotropic hormone; CD, Cushing's disease; CI, confidence interval; CS, Cushing's syndrome; mUFC, mean urinary free cortisol.

Safety

ADVERSE EVENTS

- Hepatotoxicity
- QT Prolongation
- Hypocortisolism
- Hypersensitivity Reactions
- Risks related to Decreased Testosterone

The safety of Recorlev® was evaluated in a multicenter, randomized-withdrawal study (Study 1) and in a multicenter, single-arm, open-label study (Study 2). During the two studies, 166 patients were exposed to Recorlev®, of which 104 patients were exposed for more than 6 months and 51 patients were exposed for at least 1 year. In both studies, most patients took Recorlev® twice daily in total daily dosages ranging from 300 mg to 1200 mg.

Hypocortisolism

Hypocortisolism was reported in 11 (7%) of 166 patients across Studies 1 and 2, with events starting on median study day 96 (range 26-166). The majority of cases were managed by reducing the dosage or temporarily interrupting treatment with Recorlev®.

WARNINGS & PRECAUTIONS

Hepatotoxicity: Cases of hepatotoxicity with a fatal outcome or requiring liver transplantation have been reported with the use of oral ketoconazole, the racemic mixture from which levoketoconazole is derived. Some patients had no obvious risk factors for liver disease. Serious hepatotoxicity has been reported in patients receiving Recorlev®, irrespective of the dosages used or the treatment duration. Drug-induced liver injury (peak ALT or AST greater than 3 times upper limit of normal) occurred in 13% of patients using Recorlev®.

Recorlev® is contraindicated in patients with cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT greater than 3 times the upper limit of normal, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease.

Avoid concomitant use of Recorlev® with hepatotoxic drugs. Advise patient to avoid excessive alcohol consumption while on treatment with Recorlev®.

QT Prolongation: Recorlev® is associated with dose-related QT interval prolongation. QT interval prolongation may result in life-threatening ventricular dysrhythmias such as torsades de pointes. Perform ECG prior to and during treatment.

Hypocortisolism: Hypocortisolism has been reported with Recorlev®. Lowering of cortisol levels can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, and dizziness. Significant lowering of serum cortisol levels may result in adrenal insufficiency that can be manifested by hypotension, abnormal electrolyte levels, and hypoglycemia. Monitor patients for hypocortisolism. Dosage reduction or interruption may be necessary.

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in 1% of patients treated with Recorlev®. Anaphylaxis has been reported with oral ketoconazole.

Risks Related to Decreased Testosterone: Recorlev® may lower serum testosterone in men and women. Inform patients to report associated symptoms.

CONTRAINDICATIONS

Cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT > 3 times the upper limit of normal, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease.

Taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsade's de pointes.

Prolonged QTcF interval > 470 msec at baseline, history of torsade's de pointes, ventricular tachycardia, ventricular fibrillation, or prolonged QT syndrome.

Hypersensitivity to levoketoconazole, ketoconazole or any excipient in Recorlev®.

Taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gp.

Clinical Pharmacology

MECHANISMS OF ACTION

In vitro, levoketoconazole inhibits key steps in the synthesis of cortisol and testosterone, principally those mediated by CYP11B1 (11β hydroxylase), CYP11A1 (the cholesterol side-chain cleavage enzyme, the first step in the conversion of cholesterol to pregnenolone), and CYP17A1 (17α-hydroxylase).

Dose & Administration

ADULTS

Initiate dosage at 150 mg orally twice daily, with or without food. Titrate dosage by 150 mg daily, no more frequently than every 2-3 weeks. Maximum recommended dosage is 1200 mg daily, administered as 600 mg twice daily

PEDIATRICS

None

GERIATRICS

Refer to adult dosing

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 150 mg