Pharmacy Policy Bulletin: J-1173 Recorlev (levoketoconazole) – Commercial and Healthcare Reform	
Number: J-1173	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1., 2., or 3.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-1173-004	**Original Date:** 01/26/2022
Effective Date: 02/14/2025	**Review Date:** 01/29/2025

Drugs Product(s):	• Recorlev (levoketoconazole)
FDA-Approved Indication(s):	• Treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative

Background:	• Recorlev (levoketoconazole) inhibits key steps in the synthesis of cortisol and testosterone, thereby reducing endogenous cortisol levels. Therapeutically active ketoconazole is a racemic mixture of two enantiomers, one of which is levoketoconazole. Therapeutically active levoketoconazole is the pure (2S, 4R) enantiomer.
	• Recorlev is not approved for the treatment of fungal infections.
	• Cushing's syndrome (CS) is a rare endocrine disorder resulting from an excessive amount of the hormone cortisol. There are two forms of CS, including exogenous CS [caused by long-term, high-dose exposure to cortisol like medications (for example, corticosteroids)] and endogenous CS. Endogenous causes include:
	  ○ Cushing's disease (CD) which occurs when a benign pituitary tumor (adenoma) stimulates an excessive production of adrenocorticotropin hormone (ACTH) causing an overproduction of cortisol from the adrenal glands.
	  ○ Non-pituitary tumors (benign or malignant) that secrete excessive ACTH.
	  ○ Adrenal gland tumors (benign or malignant) that secrete excessive cortisol.
	• The 2021 Pituitary Society Consensus Guideline recommends transsphenoidal surgery (TSS) as first-line therapy for patients with CD. For patients with CD for whom surgery was not an option or was not curative, the steroidogenesis inhibitors ketoconazole, osilodrostat (Isturisa), and metyrapone (Metopirone) are recommended. The dopamine receptor agonist, cabergoline may also be used but is not preferred due to lower efficacy and a slower onset of action.

	• The 2015 Endocrine Society Cushing's Syndrome guidelines also support the use of steroidogenesis inhibitors as second-line therapy following surgery. • The goal of treatment is clinical normalization using reduction of cortisol levels as a proxy endpoint. • Urinary free cortisol (UFC) measurements are used primarily in the diagnosis of hypercortisolism caused by Cushing's syndrome. In normal circumstances, less than 5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form of cortisol and is filterable by renal glomeruli. With increased levels of plasma cortisol, free cortisol levels increase, which is then filtered through the glomeruli. The concentration of plasma free cortisol correlates well with urinary free cortisol. • Prescribing Considerations: ○ The maintenance dose of Recorley is individualized and determined by titration based on UFC levels and patient's signs and symptoms. Maximum recommend dosage is 1200 mg daily. ○ Recorlev has black box warnings for hepatotoxicity and QT prolongation. ○ Recorlev is contraindicated in patients with cirrhosis, acute liver disease or poorly controlled chronic liver disease, 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. ○ Recorlev is contraindicated with other drugs that prolong the QT interval, in patients with a prolonged QTcF interval of greater than 470 msec at baseline, and in patients with a history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history).

Approval Criteria

I. Initial Authorization

When a benefit, coverage of Recorlev may be approved when all of the following criteria are met **(A. through E.)**:

A. The member must be 18 years of age or older.

B. The member has a diagnosis of endogenous Cushing's syndrome (ICD-10: E24.0 E24.3, E24.8, E24.9).

C. Recorlev is prescribed by or in consultation with an endocrinologist.

D. The member meets one (1) of the following criteria **(1. or 2.)**:

1. The member is not a candidate for surgery.

2. The member has experienced therapeutic failure to surgery (specifically, has not been curative).

E. The member has experienced therapeutic failure, contraindication, or intolerance to ketoconazole tablets.

II. Reauthorization

When a benefit, reauthorization of Recorlev may be approved when all of the following criteria are met **(A. and B.)**:

A. The member has experienced a reduction in the 24-hour mean urinary free cortisol (mUFC) levels from baseline.

B. The prescriber attests that the member has experienced an improvement in signs and symptoms of Cushing's syndrome from baseline.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Recorlev is not approved for the treatment of fungal infections
II. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.
III. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

- None

References:

1. Recorlev [package insert]. Chicago, IL: Xeris Pharmaceuticals, Inc.; June 2023.
2. RareDiseases.org. Cushing syndrome. National Organization for Rare Disorders (NORD), Inc. 2021. Available at: https://rarediseases.org/rare-diseases/cushing-syndrome/. Accessed January 14,2025.
3. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9;847-875.
4. Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(8):2807-2831.
5. Loran CS. Urinary Free Cortisol. Medscape. Available at: https://emedicine.medscape.com/article/2088848-overview. Accessed January 14,2025.

Pharmacy policies do not constitute medical advice, nor are they intended to govern physicians' prescribing or the practice of medicine. They are intended to reflect the plan's coverage and reimbursement guidelines. Coverage may vary for individual members, based on the terms of the benefit contract.

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