09-J4000-17

Original Effective Date: 10/01/22

Reviewed: 06/14/23

Revised: 07/15/23

Subject: Levoketoconazole (Recorlev) tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Cushing's syndrome is a condition of excess exposure to glucocorticoids from an endogenous or exogenous source. Cushing's syndrome can be dependent on adrenocorticotropic hormone (ACTH), and the most common form is Cushing's disease caused by the overproduction of ACTH by a pituitary tumor. Other forms are independent of ACTH which may include adrenocortical adenoma or carcinoma or nodular adrenal hyperplasia. Surgery is the first line treatment although recurrence after surgery may occur. Treatment options following recurrence include repeating surgery, radiotherapy, medication therapy, or bilateral adrenalectomy. Medication therapy may include steroidogenesis inhibitors (e.g., ketoconazole, metyrapone, mitotane), pituitary-directed treatment to inhibit ACTH secretion (e.g. cabergoline, pasireotide) or glucorcorticoid-receptor directed therapy for patients with diabetes mellitus or glucose intolerance (mifepristone). If hypercortisolism persists, complications may include metabolic symptoms, cardiovascular disorders, muscle weakness, neuropsychiatric abnormalities, and osteoporosis.

Levoketoconazole (Recorlev) is Food and Drug Administration (FDA) approved 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 inhibits steps in the synthesis of cortisol and testosterone. Levoketoconazole is the 2S, 4R enantiomer of ketoconazole.

The safety and efficacy of levoketoconazole was evalutated in two studies. The first study consisted of a 19 week open-label dose titration and maintenance phase followed by an 8 week randomized, double-blind, placebo-controlled, withdrawal phase. There were 84 enrolled patients with Cushing's syndrome with persistent or recurrent disease despite surgery, previously medically treated and untreated patients. There were 70 patients(83%) with Cushing's disease, adrenal Cushing's syndrome in 8 patients (10%), ectopic ACTH secretion for 2 patients (2%) and unknown for 4 patients. Patients with pituitary or

adrenal carcinoma were excluded. Persistence or recurrence of Cushing's syndrome was evidenced by the mean of three 24-hour urinary free cortisol (UFC) levels greater than or equal to 1.5 × upper limit of normal (ULN). Seventy-nine patients entered the dose titration and maintenance phase, and 37 patients (47%) achieved a stable therapeutic dose for at least 4 weeks and a normal mUFC. In the withdrawal phase, there were 21 patients randomized to receive levoketoconazole and 18 to receive placebo for 2 months or until early rescue was necessary (when mUFC >1.5 × ULN). The key secondary efficacy endpoint was the proportion of patients with mUFC normalization, defined as a patient with mUFC at or below the ULN at the end of randomized withdrawal phase without meeting a requirement for early rescue during the randomized withdrawal phase. Among the 39 patients who had normal mUFC at the randomized withdrawal phase baseline, the number and percent of patients who had normal mUFC at the end of the randomized withdrawal phase was 11/21 (52.4%) in the levoketoconazole group and 1/18 (5.6%) in placebo group [difference (CI) 46.8% (16.5%, 70.2%)]. Out of 11 patients with normal mUFC at the end of the randomized-withdrawal phase, 7 patients in the levoketoconazole group had normal mUFC throughout the randomized-withdrawal phase.

Supportive evidence of efficacy was obtained from Study 2 which was a multicenter, single-arm, open-label study in 94 Cushing's syndrome patients that consisted of three study phases (dose titration, maintenance, and extended evaluation) for a total of estimated treatment duration of up to 73 weeks. The primary efficacy endpoint of the study was the proportion of patients with normalization of mean UFC at or below the upper limit of normal based on central laboratory result without requiring a dose increase during maintenance phase. At the end of the maintenance phase, 30.9% of patients (95% CI interval 21.7% - 41.2%) met the primary endpoint without any dose increase. At the end or the extended evaluation phase, 17% of patients had a normal mUFC without any dose increase during the maintenance or extended evaluation phase. There were 51% of patients who discontinued treatment early due to adverse reaction, lack of efficacy, or for other reasons.

The most common adverse reactions (incidence > 20%) were nausea/vomiting, hypokalemia, hemorrhage/contusion, systemic hypertension, headache, hepatic injury, abnormal uterine bleeding, erythema, fatigue, abdominal pain/dyspepsia, arthritis, upper respiratory infection, myalgia, arrhythmia, back pain, insomnia/sleep disturbances, and peripheral edema.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of levoketoconazole (Recorlev) **meets the definition of medical necessity** when **ALL** of the following are met:

1. The member has a diagnosis of endogenous Cushing's syndrome
2. The member has persistent or recurrent disease following surgery **OR** the member is not a candidate for surgery

3. The member has a mean of three 24 hour urinary free cortisol (UFC) values > 1.5 x upper limit of normal (ULN) – documentation must be submitted
4. The member has tried and had intolerable adverse effects to ketoconazole and ALL of the following must be submitted:
    a. The specific intolerance(s) to ketoconazole and rationale for using Recorlev must be specified
    b. Completed Medwatch reporting form (FDA 3500) – https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
    c. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf
5. The member has an inadequate response, intolerance, contraindication, or is not a candidate for treatment with pasireotide (Signifor, Signifor LAR)– documentation must be submitted
6. The member does not have any of the following contraindications to levoketoconazole:
    a. Increased risk of hepatotoxocity (cirrhosis, acute liver disease or poorly controlled chronic liver disease, recurrent symptomatic cholelithiasis, metastatic liver disease, or prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy)
    b. Increased risk of QT prolongation (QTcF interval greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, prolonged QT syndrome, or taking concomitant medications that may cause QT prolongation)
    c. Hypersensitivity to levoketoconazole or ketoconazole
    d. Taking medications that are sensitive substrates of CYP3A4 or CYP3A4 and P-glycoprotein
7. ALL of the following baseline tests have been completed:
    a. Liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase, (AST), total bilirubin]
    b. serum potassium
    c. serum magnesium
    d. electrocardiogram
8. Levoketoconazole will be prescribed as a single agent
9. Levoketoconazole will be prescribed by or in consultation with an endocrinologist
10. The dosage does not exceed 600 mg twice a day

Approval duration: 6 months

Continuation of levoketoconazole (Recorlev) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has a beneficial response to treatment (e.g., normalization of urinary free cortisol) – documentation must be submitted

2. An authorization or reauthorization has been previously approved for the treatment of endogenous Cushing's syndrome by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim for Recorlev during the 90 days immediately before the authorization request must be submitted), **OR** the member has previously met all indication-specific criteria for coverage
3. The member has tried and had intolerable adverse effects to ketoconazole and **ALL** of the following must be submitted†:
    a. The specific intolerance(s) to ketoconazole and rationale for using Recorlev must be specified
    b. Completed Medwatch reporting form (FDA 3500) – https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
    c. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf
4. The member does not have any of the following contraindications to levoketoconazole:
    a. Increased risk of hepatotoxocity (cirrhosis, acute liver disease or poorly controlled chronic liver disease, recurrent symptomatic cholelithiasis, metastatic liver disease, or prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy)
    b. Increased risk of QT prolongation (QTcF interval greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, prolonged QT syndrome, or taking concomitant medications that may cause QT prolongation)
    c. Hypersensitivity to levoketoconazole or ketoconazole
    d. Taking medications that are sensitive substrates of CYP3A4 or CYP3A4 and P-glycoprotein
5. Levoketoconazole will be prescribed as a single agent
6. Levoketoconazole will be prescribed by or in consultation with an endocrinologist
7. The dosage does not exceed 600 mg twice daily

Approval duration: 6 months

†Step therapy requirement does not apply if a prior health plan paid for the medication - documentation of a paid claim within the past 90 days must be submitted

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or have not been curative:

- Initiate 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.
- Obtain baseline liver and electrocardiogram tests and correct hypokalemia and hypomagnesemia before starting levoketoconazole.
- Once the maintenance dosage is achieved, monitor cortisol levels from at least two 24 hour urine free cortisol collections at least every 1-2 months or as indicated.
- If 24-hour urine free cortisol levels remain above the upper normal limit after treatment with the maximum recommended dosage of 1200 mg per day, or the patient cannot tolerate treatment, consider discontinuation and switch to another therapy.
- For recommendations on titration, monitoring for safety, efficacy, and dose modification for hepatotoxicity, QT prolongation and hypocortisolism, see prescribing information.
- Levoketoconazole is not approved for the treatment of fungal infections.

Dose Adjustments

- The dosage may be reduced to 150 mg once daily if needed for reasons of tolerability.

Drug Availability

- 150 mg tablets

PRECAUTIONS:

Boxed Warning

Hepatotoxicity

- Cases of hepatotoxicity with a fatal outcome or requiring liver transplantation have been reported with use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Serious hepatotoxicity has been reported in patients
- Levoketoconazole 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.
- Evaluate liver enzymes prior to and during treatment. Interrupt levoketoconazole treatment immediately if signs of hepatotoxicity occur

QT Prolongation

- Levoketoconazole is associated with dose-related QT interval prolongation. QT interval prolongation may lead to life-threatening ventricular dysrhythmias such as torsades de pointes
- Coadministration of levoketoconazole with other drugs that prolong the QT interval associated with ventricular arrhythmias, including torsades de pointes, and use in patients with a prolonged QTcF

interval of greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history) are contraindicated

- Perform an ECG and correct hypokalemia and hypomagnesemia prior to and during treatment. Temporarily discontinue if QTcF interval exceeds 500 msec

Contraindications

- 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
- Taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes
    - Examples: Bosutinib, cisapride, clarithromycin, cobimetinib, crizotinib, disopyramide, dofetilide, dronedarone, eliglustat (in patients that are poor or intermediate metabolizers of CYP2D6 and in patients taking strong or moderate CYP2D6 inhibitors), ivabradine, methadone, midostaurin, nicardipine, pimozide, quinidine, and ranolazine.
- With a prolonged QTcF interval of greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history)
- With known hypersensitivity to levoketoconazole, ketoconazole or any excipient in levoketoconazole
- Taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gP
    - Examples Alfentanil, avanafil, buspirone, conivaptanb, dabigatran etexilate, darifenacin, darunavir, digoxin, ebastine, everolimus, fexofenadine, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavirb, triazolam, and vardenafil.

Precautions/Warnings

- Hypocortisolism: Hypocortisolism has been reported with levoketoconazole. Monitor patients for hypocortisolism. Dosage reduction or interruption may be necessary
- Hypersensitivity Reactions: Hypersensitivity to levoketoconazole has been reported. Anaphylaxis has been reported with oral ketoconazole
- Risks Related to Decreased Testosterone: levoketoconazole may lower serum testosterone in men and women. Inform patients to report associated symptoms.
- See black box warning for hepatotoxicity and QT prolongation

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

E24.0	Pituitary-dependent Cushing's disease
E24.3	Ectopic ACTH syndrome
E24.9	Cushing's syndrome, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Cushing's syndrome: is a hormone disorder caused by high levels of cortisol in the blood. This can be caused by taking glucocorticoid drugs, or by tumors that produce cortisol or adrenocorticotropic hormone (ACTH) or CRH.

Cushing's disease: when the pituitary gland makes too much of the hormone ACTH. ACTH then signals the adrenal glands to produce cortisol. Tumor of the pituitary gland may cause this condition.

RELATED GUIDELINES:

Osilodrostat (Isturisa), 09-J3000-74

Pasireotide (Signifor, Signifor LAR) Injection, 09-J1000-94

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2023. URL www.clinicalpharmacilogy-ip.com Accessed 06/02/23.

2. Cuevas-Ramos D, Shao Ting Lim D, Fleseriu M. Update on medical treatment for Cushing's disease. Clin Diabetes Endocrinol. 2016; 2 (16): 1-13.
3. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 06/02/23.
4. Nieman LK, Biller B, Findling JW et al. Treatment of Cushing's syndrome: An Endocrine Society Practice Guideline. J Clin Endocrinol Metab. 2015; 100(8): 2907 – 2831.
5. Recorlev (levoketoconazole) [package insert]. Xeris Pharmaceutical. Chicago (IL): Dec 2021.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/14/23.

GUIDELINE UPDATE INFORMATION:

10/01/22	New Medical Coverage Guideline.
07/15/23	Review and revision to guideline; consisting of updating the references.