levoketoconazole (Recorlev®)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO254

Description

Levoketoconazole (Recorlev®), the 2S,4R enantiomer of ketoconazole, is an orally administered steroidogenesis inhibitor that reduces endogenous cortisol levels.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
levoketoconazole (Recorlev®)	150 mg tablets	Cushing's Syndrome	240 tablets/30 days

Initial Evaluation

I. **Levoketoconazole (Recorlev)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. Levoketoconazole (Recorlev) will not be used in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or mifepristone (Korlym); **AND**
   D. A diagnosis of **Cushing's syndrome** when the following are met:
      1. Member is not a candidate for pituitary surgery; **OR**
         i. Cortisol levels remain abnormal following attempted resection; **AND**
      2. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; **OR**
         i. Documentation of serious adverse effect or allergy with oral ketoconazole; **AND**
      3. Treatment with ALL of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
         i. Cabergoline (Dostinex); **AND**
         ii. Metyrapone (Metopirone); **AND**
         iii. Mitotane (Lysodren); **AND**
         iv. Pasireotide diaspartate (Signifor)*

II. Levoketoconazole (Recorlev) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Treatment of fungal infections

III. Levoketoconazole (Recorlev) is considered investigational when used for all other conditions, including but not limited to:
   A. Exogenous (Iatrogenic) Cushing's syndrome
   B. Use in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or mifepristone (Korlym)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; **OR**
   a. Documentation of serious adverse effect or allergy with oral ketoconazole; **AND**
IV. Member has exhibited improvement or stability of cortisol levels and disease symptoms [e.g., improvement in cushingoid appearance, acne, hirsutism, psychiatric symptoms, body weight].

Supporting Evidence

I. Ketoconazole is a racemic mixture of two enantiomers, one of which is levoketoconazole. Levoketoconazole (Recorlev) is the pure (2S, 4R) enantiomer and is FDA approved for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom pituitary surgery is not an option or has not been curative.
II. The safety and efficacy of levoketoconazole (Recorlev) has been studied in patients 18 years of age or older, and there is no published data to support its use in pediatric patients.
III. Cushing's syndrome is a disorder that leads to excess cortisol (hypercortisolemia) and is usually due to a corticotropin (ACTH)-producing pituitary or adrenal tumor. Hallmark symptoms of high levels of cortisol include clinical features such as weight gain, hypertension, high blood glucose, and depression. Goals of treatment include the reversal of clinical manifestations by normalizing cortisol secretion, damaging tumor eradication, and avoidance of permanent hormone deficiency which can result in dependence upon medications. Diagnosis and management of

Cushing's syndrome is complex and requires confirmatory tests (e.g., urinary free cortisol (UFC), salivary cortisol) as well as close monitoring by, or in consultation with, an endocrinologist.

IV. According to the Endocrine Society Clinical Practice Guidelines and Pituitary Society Consensus Guidelines for Cushing's disease, first line treatment for excess cortisol production due to Cushing's syndrome is transsphenoidal surgery (TSS) regardless of the cause. Although surgical treatment is optimal with a success rate of 80-85%, second-line medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Repeat TSS is indicated in patients with recurrent Cushing's syndrome symptoms and have evidence of residual visible tumor on MRI. There is low quality evidence recommending systemic therapy to treat Cushing's syndrome in the pre-operative setting. Pre-operative therapy with systemic treatment or targeted radiation may be considered for patients with aggressive Cushing's syndrome, defined as those with life-threatening severe clinical features to rapidly reduce or stabilize cortisol levels.

V. Systemic therapy options for Cushing's syndrome consist of steroidogenesis inhibitors (i.e., ketoconazole, metyrapone, mitotane, osilodrostat, etomidate), pituitary-directed agents (i.e., cabergoline, pasireotide), and glucocorticoid antagonists (i.e., mifepristone). Only levoketoconazole (Recorlev), osilodrostat, and pasireotide are FDA-approved to treat Cushing's syndrome/disease in patients who pituitary surgery is not an option or has not been curative. Ketoconazole, metyrapone, mitotane, etomidate, and cabergoline are used off-label for Cushing's syndrome.

VI. Guidelines recommend steroidogenesis inhibitors (i.e., ketoconazole, osilodrostat, metyrapone, etomidate) as first-line pharmacologic therapy following non-curative surgery or in patients for whom surgery was not an option. Among these therapies, ketoconazole is strongly recommended due to ease of dose titration and availability. Efficacy of ketoconazole in Cushing's syndrome is based on several retrospective trials that report UFC normalization in 45-50% of patients. IV anesthetic, etomidate has a rapid onset of action, but use is limited to acute treatment of severe hypercortisolism due to Cushing's syndrome. Second-line systemic therapies may include any of the remaining agents (i.e., pituitary-directed agents, glucocorticoid antagonists, etc.) as treatment selection is individualized based on severity of disease, clinical manifestations, cost, drug accessibility, and safety profile. As of March 2022, guidelines have not been updated with regard to place in therapy for levoketoconazole for the treatment of Cushing's syndrome.

VII. There is a lack of head-to-head trials showing superior safety or efficacy comparing levoketoconazole to ketoconazole, cabergoline (Dostinex), metyrapone (Metopirone), mitotane (Lysodren), or pasireotide diaspartate (Signifor). Given the known safety, established efficacy, and cost-effectiveness of these therapies, trial of all of these regimens is required prior to use of levoketoconazole (Recorlev).

VIII. Guidelines do not specify a preferred treatment algorithm, nor do they indicate that treatment failure to one agent precludes treatment with another agent in the same class. The Pituitary

Society guidelines recommend switching therapies when cortisol levels remain elevated despite treatment on maximum tolerated dose for 2-3 months. Retrospective studies and clinical trials evaluated treatment response at 6-months while patients were maintained on a stable therapeutic dose. In absence of strong evidence to support a preferred treatment algorithm, trial of oral ketoconazole at a maximally tolerated therapeutic dose for at least three-months is required prior to assessing treatment failure.

IX. Levoketoconazole (Recorlev) has not been evaluated against ketoconazole for the treatment of hypercortisolemia in patients with Cushing's syndrome therefore comparative safety and remain uncertain. However, the chemical entity in ketoconazole is the same as levoketoconazole (Recorlev); therefore, both products are expected to produce a similar efficacy and safety profile for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome, even in the absence of an FDA-labeled indication for ketoconazole. Further, medical necessity for levoketoconazole (Recorlev) is limited to members that have a documented serious intolerance (e.g., allergy reaction, serious adverse event, life-threatening reaction that required hospitalization) or treatment failure with generic oral ketoconazole. If a member has a contraindication to ketoconazole, it is presumed that treatment with levoketoconazole would also be contraindicated, given similar warnings and side effect profile.

X. Levoketoconazole (Recorlev) has been studied in two phase 3 studies for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom pituitary surgery is not an option or has not been curative.

- The SONICS trial was a 6-month open-label, single arm, dose-titration study (n=95) with a 21-week run-in period; patients who did not achieve a stable therapeutic dose during this dose titration phase did not continue in the study. The primary efficacy endpoint was the proportion of patients with normalized mean urinary free cortisol (mUFC) response of at the end of a 6-month maintenance phase without a dose increase. About 30% of patients on levoketoconazole achieved a normalized mUFC (95% CI: 21.7%- 41.2%; p=0.0154) at 6 months. Significant mean improvements in comorbidity biomarkers and clinical signs and symptoms were also seen (glucose metabolism, total cholesterol, LDL, HDL, body weight, and hirsutism (women)). Approximately 15% of patients had at least one treatment-related serious adverse event, which include reversible liver-related adverse events, QT prolongation, and adrenal insufficiency. Routine laboratory assessments showed ALT increases above the ULN in 41% of patients at any time. Notably, 51% of study participants discontinued therapy with the most common reasons being adverse events and inefficacy.
- The LOGICS trial was 6-month double-blind, randomized, placebo-controlled withdrawal and rescue/restoration study of patients who completed the SONICS trial (n=12) or were treatment-naïve (n=72). A total of 84 patients were enrolled in the study, of whom 44 entered the randomized withdrawal phase and were

assigned 1:1 to placebo or levoketoconazole. The primary outcome was the proportion of patients with loss of mUFC response, which was met with a 40% loss of response in the levoketoconazole group compared to 95% of patients in the placebo group (p=0.0002). A secondary endpoint, mUFC normalization, was met with 50% of patients achieving normalized mUFC in the levoketoconazole group compared to 4.5% of patients on placebo (95% CI: 19.2-67.9; P=0.0015). Approximately 48% of patients discontinued the study before the double-blind phase due to treatment related adverse events. Additionally, 95% of patients required rescue therapy due to high mUFC levels during the randomized withdrawal phase.

- Long term safety and efficacy of levoketoconazole has not been established; however, an ongoing trial (OPTIC study) is currently evaluating long-term use of levoketoconazole in patients that have completed the SONICS and LOGICS trials.
- The overall quality of evidence for levoketoconazole (Recorlev) is considered low due to open-label study design, lack of a comparator or meaningful comparator given high volume of concomitant rescue therapy, and high attrition rate. While UFC is a clinically meaningful, objective endpoint correlated with improvement of hypercortisolism in Cushing's syndrome, concerns listed above limit confidence that medication is providing a clinically meaningful benefit over available treatments for Cushing's syndrome. Additionally, levoketoconazole use was associated with serious safety concerns including hepatotoxicity and QT prolongation.

Investigational or Not Medically Necessary Uses

I. Levoketoconazole (Recorlev) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Treatment of fungal infections
      i. Safety and efficacy of levoketoconazole (Recorlev) has not been established for treating fungal infections and should not be substituted for ketoconazole when used to treat fungal infections. Additionally, drugs or interventions that a treating licensed health care provider recommends are considered medically necessary if the level of service, intervention, or prescription drug recommended for the condition is cost-effective compared to alternative interventions.
   B. Exogenous (Iatrogenic) Cushing's syndrome
      i. Safety and efficacy has only been established for endogenous Cushing's syndrome, there is currently limited evidence to suggest the use of levoketoconazole in the setting of exogenous (iatrogenic) Cushing's syndrome.

C. Used in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or mifepristone (Korlym)
    i. In practice, ketoconazole has been used in combination with metyrapone or with osilodrostat to maximize cortisol level lowering when monotherapy has been ineffective; triple therapy (ketoconazole/pasireotide/cabergoline and ketoconazole/metyrapone/mitotane) has also been used in patients with uncontrolled cortisol levels and presence of visible tumor post-resection. However, quality of evidence supporting combination use is low and there are significant safety concerns due to additive toxicity (QT prolongation, hepatotoxicity).
    ii. Levoketoconazole (Recorlev) has not been studied in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or mifepristone (Korlym).

Appendix

I. The recommended initial dosing of levoketoconazole is 150 mg twice daily and dosing is titrated by 150 mg daily every 2-3 weeks until an adequate clinical response is achieved based on cortisol levels and patient tolerability. The maximum recommended dosage is 1,200 mg per day in divided doses.

II. Levoketoconazole (Recorlev) carries black box warning for hepatotoxicity and is contraindicated in patients with cirrhosis, elevated LFT defined as baseline AST or ALT > 3 times the upper limit of normal, acute liver disease or poorly controlled chronic liver disease, extensive metastatic liver disease, or recurrent symptomatic cholelithiasis. Cases of serious hepatoxicity were reported in patients taking levoketoconazole (Recorlev) and therefore treatment with levoketoconazole (Recorlev) is contraindicated in patients with a prior history of drug induced liver injury with ketoconazole or any azole antifungal therapy that required treatment discontinuation (serious and fatal hepatotoxicity have been reported in patients taking oral ketoconazole). Baseline liver function tests should be obtained prior to starting therapy and continuously monitored throughout treatment.

III. Levoketoconazole (Recorlev) also carries a black box warning for QT prolongation and 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 torsade's de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history). A baseline electrocardiogram (ECG) function test should be obtained prior to starting therapy.

References

1. Recorlev [Prescribing Information]. Xeris Pharmaceuticals, Inc: Chicago, IL. December 2021.
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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(12):847-875. doi:10.1016/S2213-8587(21)00235-7
4. American Association of Neurological Surgeons. Cushing's Syndrome/Disease. (n.d.). Retrieved February 14, 2022, from https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Cushings-Disease
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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
osilodrostat (Isturisa®)	Cushing's disease
pasireotide diaspartate (Signifor®)	Cushing's disease
	Acromegaly Cushing's disease
mifepristone (Korlym®)	Hyperglycemia secondary to hypercortisolism in Cushing's syndrome

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	03/2022