Recorlev (levoketoconazole) Prior Authorization with Quantity Limit Program Summary

This program applies to Medicaid.

The BCBS MN Step Therapy Supplement applies to this program for Medicaid.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
1/1/2024	9/1/2022

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Recorlev® (levoketoconazole) Tablet	Treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative Limitations of use: Recorlev is not approved for the treatment of fungal infections		

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Cushing's syndrome	Cushing's syndrome denotes pathologic hypercortisolism as a result of excessive adrenocorticotropic hormone (ACTH) production or autonomous adrenal production of cortisol. This potentially lethal disorder is associated with significant comorbidities including hypertension, diabetes, coagulopathy, cardiovascular disease, infections, and fractures. As a result, even after cure of hypercortisolism, mortality rates may be increased. Because of this it is important to make the diagnosis as early in the disease course as possible to prevent additional morbidity and residual disease. Signs and symptoms of Cushing's syndrome are broad and often common among the general population such as obesity, depression, diabetes, hypertension, or menstrual irregularities. Some features are more discriminatory and unique to Cushing's syndrome such as reddish-purple striae, plethora, proximal muscle weakness, bruising with no obvious trauma, and unexplained osteoporosis.(2) Cushing's disease is a form of Cushing syndrome. Cushing's disease occurs when a benign tumor in the pituitary gland causes the pituitary gland to produce too much ACTH. Cushing's disease can also occur with diffuse growth of the pituitary gland (pituitary hyperplasia). Pituitary hyperplasia can lead to the release of too much ACTH which then leads to over-production of cortisol by the adrenal glands.(2) Diagnosis of Cushing's syndrome is often delayed for years, partly because of lack of awareness of the insidious progressive disease process and testing complexity. Screening and diagnostic tests for Cushing's syndrome assess cortisol secretory status: abnormal circadian rhythm with late-night salivary cortisol (LNSC), impaired

	glucocorticoid feedback with overnight 1 mg dexamethasone suppression test (DST) or low-dose 2-day dexamethasone test (LDDT), and increased bioavailable cortisol with 24-hour urinary free cortisol (UFC). The sensitivity of all tests is higher than 90%; the highest sensitivity rates are obtained with DST and LNSC and the lowest with UFC. Specificity is somewhat lower than sensitivity, with LNSC being the most specific and DST and UFC the least specific. LNSC should not be used in patients with disruption of normal day and night cycle, such as night-shift workers.(3) Clinical considerations and recommendations for Cushing's syndrome diagnosis and monitoring of Cushing's disease recurrence:(3) • If Cushing's syndrome is suspected: o Start with UFC, LNSC or both; DST could be an option if LNSC is not feasible o Multiple LNSC might be easier for patient collection • If confirming Cushing's syndrome: o Can use any test o UFC (average 2 or 3 collections) above the upper limit of normal – cutoff is assay-specific reference range o LNSC (2 or more tests) above the upper limit of normal – cutoff is assay-specific reference range o DST useful in night-shift workers, not in women on estrogen containing contraceptives – above cutoff of 1.8 mcg/dL o Measuring dexamethasone concentration, with cortisol concentration the morning after 1 mg dexamethasone ingestion improves interpretability • If Cushing's syndrome due to adrenal tumor is suspected o Start with DST as LNSC has lower specificity in these patients • Monitoring for recurrence: o Consider which tests were abnormal at initial diagnoses o LNSC most sensitive and should be done annually – above cutoff of 0.27 mcg/dL o DST and UFC usually become abnormal after LNSC (with UFC usually the last to become abnormal) o UFC 1.6 X upper limit of normal o DST above 1.8 mcg/dL Transsphenoidal surgery is recommended as first-line therapy for patients with Cushing's disease. Remission, typically defined as postoperative serum cortisol concentrations lower than 2 mcg/dL, is seen in approximately 80% of patients with microadenomas and 60% with macroadenomas if the procedure is performed by an experienced surgeon. Patients in remission require glucocorticoid replacement until HPA axis recovery. As remission could be delayed, monitoring until postoperative cortisol nadir can usually identify such cases.(3)

	Recurrence after successful pituitary surgery is characterized as the reappearance of clinical and biochemical features of hypercortisolism after initial remission. Published recurrence rates vary between 5% and 35% with half of recurrences appearing within the first 5 years after surgery and half after up to 10 years or more. Compared with use in the initial diagnosis of Cushing's syndrome, LNSC, DST, UFC, and desmopressin tests have a lower sensitivity for recurrence, but specificity is high. Repeat transsphenoidal surgery can be considered in patients with biochemical evidence of recurrent Cushing's disease with visible tumor on MRI.(3) Medications used for the treatment of Cushing's disease target adrenal steroidogenesis, somatostatin, and dopamine receptors in the pituitary gland, and glucocorticoid receptors.(3) • Adrenal steroidogenesis inhibitor agents o Ketoconazole 400-1600 mg total per day European Medicines Agency (EMA) approved off-label use in USA o Osilodrostat 4-14 mg total per day FDA approved o Metyrapone 500 mg to 6 g total per day EMA approved off-label use in USA o Mitotane 500 mg to 4 g total per day approved by EMA off label use in USA o Etomidate 0.04 – 0.1 mg/kg/h Off-label use only o Levoketoconazole 300-1200 mg total per day FDA approved and EMA indicated • Somatostatin receptor ligands o Pasireotide 0.6-1.8 mg/mL widely approved o Pasireotide long-acting 10-30 mg/month widely approved • Dopamine receptor agonists o Cabergoline 0.5-7 mg total per week off-label use only • Glucocorticoid receptor blocker o Mifepristone 300-1200 mg total per day FDA-approved for hyperglycemia associated with Cushing's syndrome. There are several factors helpful in selection of medical therapy:(3) • If there is a need for rapid normalization of cortisol adrenal steroidogenesis inhibitors are recommended. Osilodrostat and metyrapone have the fastest action and etomidate can be used in very severe cases (high quality, strong recommendation) • In mild disease, if residual tumor is present and there is a potential for tumor shrinkage, consider pasireotide or cabergoline (moderate quality, strong recommendation) • If there is a history of bipolar or impulse control disorder, consider avoiding cabergoline (moderate quality, strong recommendation) • If an expert pituitary endocrinologist is not available to monitor treatment response, use mifepristone cautiously (low quality, discretionary recommendation)

	• In pregnant women or those desiring pregnancy, consider cabergoline or metyrapone (low quality, strong recommendation), although no Cushing's disease medications are approved for use in pregnancy • Drug intolerance or side-effects, as well as concomitant comorbidities such as type 2 diabetes and hypertension should further guide type of medication used (moderate quality, strong recommendation) • Consider cost and estimated therapy duration, especially if definitive treatment (i.e., pituitary or adrenal surgery) is planned or while awaiting effects of radiotherapy (low quality, discretionary recommendation) Adrenal steroidogenesis inhibitors are usually used first given their reliable effectiveness. For patient with mild disease and no visible tumor on MRI, ketoconazole, osilodrostat, or metyrapone are typically preferred. For patients with mild-to-moderate disease and some residual tumor, there might be a preference for cabergoline or pasireotide because of the potential for tumor shrinkage. For patients with severe disease, rapid normalization of cortisol is the most important goal. With osilodrostat and metyrapone, response will typically be seen within hours, and with ketoconazole within a few days.(3) Change in treatment should be considered if cortisol levels are persistently elevated after 2-3 months on maximum tolerated doses. If cortisol does not normalize but is reduced or there is some clinical improvement, combination therapy can be considered (low quality, discretionary recommendation). Many experts consider combining ketoconazole with metyrapone or potentially ketoconazole with osilodrostat to maximize adrenal blockade when monotherapy is not effective, or to allow lower doses of both drugs (low quality, discretionary recommendation). Ketoconazole plus cabergoline or pasireotide, and pasireotide plus cabergoline could be rational combinations if there is visible tumor present (low quality, discretionary recommendation). Other combinations that can be used include triplets of cabergoline, pasireotide, plus ketoconazole, and ketoconazole, metyrapone, plus mitotane (low quality, discretionary recommendation).(3) Radiotherapy is primarily used as adjuvant therapy for patients with persistent or recurrent disease after transsphenoidal surgery or for aggressive tumor growth.(3)
Efficacy(1)	Recorlev (levoketoconazole) contains the 2S,4R-enantiomer derived from racemic ketoconazole and is a cortisol synthesis inhibitor. The effectiveness of Recorlev in patients with Cushing's syndrome was evaluated in two studies (labeled Study 1 and Study 2). Study 1 (NCT03277690) consisted of an open-label dose titration and maintenance phase of up to 19 weeks duration, followed by an 8-week double blind, placebo-controlled, randomized withdrawal phase. Persistence or recurrence of Cushing's syndrome was evidenced by the mean of three 24-hour UFC levels greater than or equal to 1.5 X upper limit of normal.

	The key secondary efficacy endpoint was the proportion of patients with mean UFC normalization, defined as a patient with mean UFC at or below the ULN at the end of the randomized withdrawal phase without meeting a requirement for early rescue during the randomized withdrawal phase. The percent of patients who had normal mean UFC at the end of the randomized withdrawal phase was 52.4% in the Recorlev group and 5.6% in the placebo group, and the treatment difference (CI) was 46.8%. Supportive evidence of efficacy was obtained from Study 2 (NCT01838551) which was a multicenter, single-arm, open-label study 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% exact confidence interval) met the primary endpoint.
Safety(1)	• Recorlev contains a boxed warning with the following: ○ Cases of hepatotoxicity with fatal outcome or requiring liver transplantation have been reported with oral ketoconazole. Evaluate liver enzymes prior to and during treatment ○ Recorlev is associated with dose-related QT interval prolongation. Perform ECG prior to and during treatment • 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 ○ Patients taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes ○ Patients with prolonged QT_cF interval greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or prolonged QT syndrome ○ Patients with hypersensitivity to levoketoconazole, ketoconazole or any excipient in Recorlev ○ Patients taking certain that are sensitive substrates of CYP3A4 or CYP3A4 and P-gp

REFERENCES

Number	Reference
1	Recorlev Prescribing Information. Xeris Pharmaceuticals, Inc. December 2021.
2	Endocrine Society. Cushing's disease. Accessed at: https://www.hormone.org/diseases-and-conditions/cushings-disease

Number	Reference
3	Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol December 2021;9 847-75.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Recorlev	Levoketoconazole Tab	150 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Recorlev	Levoketoconazole Tab	150 MG	240	Tablets	30				

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Recorlev	Levoketoconazole Tab	150 MG	Medicaid

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Recorlev	Levoketoconazole Tab	150 MG	Medicaid

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of Cushing's syndrome **AND** 2. ONE of the following: A. The patient had an inadequate response to pituitary surgery **OR** B. The patient is NOT a candidate for pituitary surgery **AND** 3. The patient's disease is persistent or recurrent as evidenced by ONE of the following: A. The patient has a mean of three 24-hour urine free cortisol (UFC) greater than 1.5 times the upper limit of normal **OR** B. Morning plasma adrenocorticotropic hormone (ACTH) above the lower limit of normal **AND** 4. ONE of the following: A. The patient's medication history includes a conventional agent (i.e., Mifepristone, Signifor/Signifor LAR (pasireotide), Isturisa (osilodrostat), Cabergoline Metyrapone or Lysodren (mitotane) AND ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has had an inadequate response to conventional agents **OR** 2. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over mifepristone, pasireotide AND osilodrostat **OR** B. The patient has an intolerance or hypersensitivity to mifepristone, pasireotide, or osilodrostat **OR** C. The patient has an FDA labeled contraindication to mifepristone, pasireotide AND osilodrostat **OR** D. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** E. The prescriber has provided documentation that mifepristone, pasireotide AND osilodrostat cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** 5. ONE of the following: A. The patient's medication history includes ketoconazole tablets AND ONE of the following: 1. The patient has had an inadequate response to ketoconazole tablets **OR** 2. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over ketoconazole tablets **OR** B. The patient has an intolerance or hypersensitivity to ketoconazole tablets that is NOT expected to occur with the requested agent (medical records required) **OR** C. The patient has an FDA labeled contraindication to ketoconazole tablets that is NOT expected to occur with the requested agent (medical records required) **OR** D. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** E. The prescriber has provided documentation that ketoconazole tablets cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** 6. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The patient will NOT be using the requested agent in combination with glucocorticoid replacement therapy **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria. **Renewal Evaluation** **Target Agent** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with glucocorticoid replacement therapy **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for Requested Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **Length of Approval:** Initial - 6 months Renewal - 12 months