Drug Coverage Policy

Effective Date.....8/1/2024
Coverage Policy Number.....IP0389
Policy Title.....Recorlev

Cushing's – Recorlev

- Recorlev® (levoketoconazole tablets - Xeris)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

Overview
Recorlev, a cortisol synthesis inhibitor, is indicated for the treatment of endogenous hypercortisolemia in adults with **Cushing's syndrome** for whom surgery is not an option or has not been curative. Recorlev was approved through the 505(b)(2) pathway and as such relied upon existing safety and efficacy information for ketoconazole tablets to support approval. Recorlev contains levoketoconazole as the active ingredient. Levoketoconazole is the 2S, 4R-enantiomer derived from racemic ketoconazole.

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. Treatment for Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[4]

Guidelines
The Endocrine Society published clinical practice guidelines (2015) for the treatment of Cushing's syndrome.[5] Recorlev is not addressed in the guidelines. First-line treatment involves resection of the tumor unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid levels. In patients with ACTH-dependent Cushing's syndrome who underwent non-curative surgery or for whom surgery was not possible, the guidelines advocate several second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy). For Cushing's disease, the guidelines recommend all medical therapies as second-line options after transsphenoidal surgery: steroidogenesis inhibitors (ketoconazole, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets], etomidate) in patients either with or without radiotherapy/radiosurgery; pituitary-directed medical treatments (cabergoline, Signifor® [pasireotide subcutaneous injection]) in patients who are not surgical candidates or who have persistent disease; and Korlym® (mifepristone tablets) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal surgery.

A 2021 guideline update does recognize Recorlev as an investigational drug for the treatment of Cushing's syndrome, but do not give recommendations for therapy placement within existing medications.[6]

Medical Necessity Criteria

Recorlev is considered medically necessary when the following is met:

FDA-Approved Indication

1. **Endogenous Cushing's Syndrome.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has hypercortisolemia; AND
   - **C)** Patient meets ONE of the following (i, ii, OR iii)
     a. According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; OR
     b. Patient is awaiting surgery for **endogenous Cushing's Syndrome**; OR
     c. Patient is awaiting therapeutic response after radiotherapy for **endogenous Cushing's Syndrome**; AND
   - **D)** Patient has tried ketoconazole tablets; AND
   - **E)** The medication is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Fungal Infections.** Recorlev is not approved for the treatment of fungal infections.[1]

References

1. Recorlev® tablets [prescribing information]. Chicago, IL: Xeris; June 2023.
2. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281–293.
3. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. *Discov Med*. 2012;13(69):171-179.
4. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: A consensus statement. *J Clin Endocrinol Metab*. 2008;93:2454-2462.
5. Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.
6. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021 Dec;9(12):847-875.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	• Updated title of policy; previously was Levoketoconazole. • **Endogenous Cushing's Syndrome:** Removed "Endogenous Cushing's Disease (pituitary origin only)", removed the preferred product box, relocated the requirement for a step through ketoconazole, and updated approval duration for Endogenous Cushing's Syndrome from 6 months to now be 12 months.	6/1/2024
Annual Revision	**Endogenous Cushing's Syndrome**: Criteria that patient who is awaiting surgery for endogenous Cushing's Syndrome or awaiting therapeutic response after radiotherapy for endogenous Cushing's Syndrome were added. **Endogenous Cushing's Syndrome – Patient Awaiting Surgery:** This condition was removed from the policy and is now addressed under Endogenous Cushing's Syndrome. **Endogenous Cushing's Syndrome – Patient Awaiting Therapeutic Response After Radiotherapy:** This condition was removed from	8/1/2024

	the policy and is now addressed under Endogenous Cushing's Syndrome.	

The policy effective date is in force until updated or retired.