Clinical Policy: Levoketoconazole (Recorlev)

Reference Number: CP.PMN.275
Effective Date: 06.01.22
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Levoketoconazle (Recorlev®) is a cortisol synthesis inhibitor.

FDA Approved Indication(s)

Recorlev is indicated for cortisol synthesis inhibitor indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome (CS) for whom surgery is not an option or has not been curative.

Limitation(s) of use: Recorlev is not approved for the treatment of fungal infections.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Recorlev is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cushing's Syndrome (must meet all)**:**

1. Diagnosis of CS;
2. Prescribed by or in consultation with an endocrinologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Surgery has not been curative;
   b. Member is not eligible for surgery;
5. Failure of ketoconazole, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 1,200 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Cushing's Syndrome (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy (*see Appendix D*);
3. If request is for a dose increase, new dose does not exceed 1,200 mg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies –

CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CS: Cushing's syndrome
FDA: Food and Drug Administration
UFC: urinary free cortisol

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ketoconazole*	400 to 1,600 mg PO daily, administered BID or TID	1,600 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Cirrhosis, acute liver disease or poorly controlled liver disease
  - Baseline aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 30 times the upper limit of normal
  - Recurrent symptomatic cholelithiasis
  - Prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy
  - Taking drugs that cause QT prolongation associated with ventricular arrhythmias
- Boxed warning(s): hepatotoxicity, QT prolongation

Appendix D: General Information

- Positive treatment response for CS includes, but is not limited to, normalization of cortisol levels or action at its receptors to eliminate signs and symptoms of the disease. A 24-hour urinary free cortisol (UFC) level may be used to assess normalization of cortisol levels. The American Association of Neurological Surgeons notes that UFC levels higher than 50-100 mcg/24 h in adults suggest the presence of CS. Dexamethasone suppression test or late night salivary cortisol concentrations may also be used to assess normalization of cortisol levels.
- The use of ketoconazole for the treatment of CS is considered off-label. However, ketoconazole is known to block multiple adrenal enzymes which is its understood mechanism in the treatment of CS. Ketoconazole is recommended as a second-line treatment by the 2015 Endocrine Society Clinical Practice Guidelines with moderate quality of evidence as a steroidogenesis inhibitor, and is also endorsed by the 2021 Pituitary Society Guideline Update.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CS	Starting dose is 150 mg PO BID. May increase by 150 mg daily, no more frequently than 2-3 weeks based on 24-hour urine free cortisol levels and patient tolerability	1,200 mg/day, administered as 600 mg BID

VI. Product Availability

Tablet: 150 mg

VII. References

1. Recorlev Prescribing Information. Chicago, IL: Xerix Pharmaceuticals, Inc.; June 2023. Available at: https://www.recorlev.com. Accessed January 24, 2025.
2. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: An Endocrine Society Clinical practice guideline. J Clin Endocrinol Metab. 2015;100(8):2807-2831.
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.
4. Cushing's syndrome/disease. American Association of Neurological Surgeons. Available at https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Cushings-Disease. Accessed February 8, 2024.
5. Pivonello R, Elenkova A, Fleseriu M, et al. Levoketoconazole in the treatment of patients with Cushing's syndrome and diabetes mellitus: Results from the SONICS phase 3 study. Front Endocrinol (Lausanne). 2021;12:595894. Published 2021 Apr 7.
6. ClinicalTrials.gov. Study to assess the safety and efficacy of levoketoconazole in the treatment of endogenous Cushing's syndrome. Available at: https://clinicaltrials.gov/ct2/show/NCT03277690. Accessed February 8, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.25.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.07.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	01.23.23	05.23
2Q 2024 annual review: no significant changes; references reviewed and updated.	02.08.24	05.24
2Q 2025 annual review: no significant changes; references reviewed and updated.	02.03.25	05.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and

accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.