

Clinical Policy: Levoketoconazole (Recorlev)

Reference Number: ERX.NPA.165

Effective Date: 06.01.22

Last Review Date: 05.22

Line of Business: Commercial, Medicaid

[Revision Log](#)

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

Description

Levoketoconazole (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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions[™] 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 \geq 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

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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

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 policy – ERX.PA.01 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 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.

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.; December 2021. Available at: www.recorlev.com/full-prescribing-information.pdf. Accessed January 14, 2022.
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 January 14, 2022.
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 January 14, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.25.22	05.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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