Original Effective Date: 04/28/2022
Current Effective Date: 10/09/2025
Last P&T Approval/Version: 07/30/2025
Next Review Due By: 07/2026
Policy Number: C23359-A

Recorlev (levoketoconazole)

PRODUCTS AFFECTED

Recorlev (levoketoconazole)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Cushing's Syndrome

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. CUSHING'S SYNDROME:
   1. Documented diagnosis of endogenous Cushing's Syndrome
      AND
   2. Documentation that Cushing syndrome specific surgery has not been curative or member is not a candidate for surgery
      AND

3. Prescriber attests that hypokalemia and hypomagnesemia have been corrected and a baseline electrocardiogram has been done prior to starting Recorlev (levoketoconazole) therapy per labeled recommendations
   AND
4. Documentation of trial (12 weeks) and failure, serious side effects, or contraindication to ketoconazole therapy
   AND
5. Documentation of baseline elevated urinary free cortisol
   AND
6. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Recorlev (levoketoconazole) include: 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; taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes; prolonged QTcF interval of greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history); hypersensitivity to levoketoconazole, ketoconazole or any excipient in Recorlev; and, taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gp]

CONTINUATION OF THERAPY:

A. CUSHING'S SYNDROME:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (e.g., hepatotoxicity, QT prolongation, hypocortisolism)
   AND
3. Documentation member has had a decrease in urinary free cortisol from baseline levels

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:

Initial Dose: 150 mg twice daily, titrated by 150 mg daily, no more frequently than every 2-3 weeks
Maximum Quantity Limits – 1200 mg daily

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Cortisol Synthesis Inhibitors

FDA-APPROVED USES:
Indicated for the 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.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Cushing syndrome is a disorder that is the result of having too much cortisol. Endogenous Cushing syndrome is rare. Endogenous causes may be adrenocorticotropic hormone (ACTH) dependent (e.g., pituitary adenoma, ectopic secretion by non-pituitary tumor) or ACTH-independent (e.g., nodular adrenal hyperplasia, adrenocortical adenoma or carcinoma). Effective treatment of Cushing syndrome to normalize cortisol levels is needed to reduce mortality and associated comorbidities. Cortisol-dependent comorbidities include psychiatric disorders, diabetes, hypertension, hypokalemia, and dyslipidemia. First line treatment is surgical resection. Second line treatments may include bilateral adrenalectomy, radiation therapy, and medications.

The choice of second line medical treatment depends on patient specific factors. The medical options may include:

- Adrenal-blocking (to reduce adrenal steroidogenesis): ketoconazole, metyrapone, Isturisa
- Pituitary-directed (centrally acting agents that suppress ACTH secretion by the pituitary; dopamine agonist: cabergoline and the somatostatin analog: pasireotide): cabergoline, pasireotide
- Glucocorticoid receptor-antagonizing drugs (blocks the peripheral effects of glucocorticoids): mifepristone

The Endocrine Society Clinical Practice Guideline for the Treatment of Cushing's Syndrome (2015, reference 4) indicate that the most appropriate therapy will depend on etiology and patient specific factors.
Recorlev (levoketoconazole) is pure 2S,4R enantiomer of ketoconazole. Recorlev was studied in the LOGICS trial (registered with ClinicalTrials.gov, NCT03277690) and SONICS trial (registered with ClinicalTrials.gov, NCT01838551). Levoketoconazole was assessed for safety and efficacy in adults with endogenous Cushing's syndrome with persistence or recurrence despite surgery. In the SONICS trial participants had a mean 24-h urinary free cortisol (mUFC) of at least 1.5 times the upper limit of normal. The primary outcome measure for SONICS was the proportion of study participants with mUFC normalization at the end of the maintenance phase of the study. 29 of the 94 participants met the primary endpoint (95% CI: 21.7%, 41.2%).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Recorlev (levoketoconazole) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Recorlev (levoketoconazole) include: 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; taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes; prolonged QTcF interval of greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history); hypersensitivity to levoketoconazole, ketoconazole or any excipient in Recorlev; and, taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gp.

Exclusions/Discontinuation:
Permanently discontinue Recorlev treatment immediately if AST or ALT exceeds or is equal to 5 times the upper limit of normal, or AST or ALT exceeds or is equal to 3 times the upper limit of normal and total bilirubin concentration increases to more than 2 times the upper limit of normal.
For AST or ALT elevations less than 3 times the upper limit of normal, or AST or ALT elevations equal to or greater than 3 to less than 5 times the upper limit of normal and total bilirubin concentration less than 2 times the upper limit of normal, monitor liver tests and manage hepatotoxicity with Recorlev dosage interruption or modifications. If a liver abnormality significantly above the patient's baseline recurs after restarting Recorlev, permanently discontinue Recorlev.
Obtain a baseline QT interval measurement and regularly monitor ECG for an effect on the QT interval during Recorlev treatment. Correct hypokalemia and/or hypomagnesemia prior to Recorlev initiation and monitor periodically during treatment. Temporarily discontinue Recorlev if the QTcF interval exceeds 500 msec. After the QTcF interval returns to less than 500 msec and contributing factors are corrected, re-institution of Recorlev at a lower dose may be considered. If QT interval prolongation recurs after restarting Recorlev, permanently discontinue Recorlev.
Decrease the dosage or temporarily discontinue Recorlev if urine free cortisol or morning blood cortisol levels fall below the target range, there is a rapid decrease in cortisol levels, or if signs and/or symptoms consistent with hypocortisolism are reported. Stop Recorlev and administer exogenous glucocorticoid replacement therapy if morning serum or plasma cortisol levels are below target range and signs and/or symptoms of adrenal insufficiency, or hypocortisolism, are present.

OTHER SPECIAL CONSIDERATIONS:
Pregnant women and females of reproductive potential should be advised of the potential risk to the fetus with use of Recorlev (levoketoconazole). Member's should be advised not to breastfeed during treatment with Recorlev (levoketoconazole) and for one day following the final dose.

Recorlev (levoketoconazole) has the following BLACK BOX WARNINGS for hepatotoxicity and QT prolongation:

1. Cases of hepatotoxicity with fatal outcome or requiring liver transplantation have been reported with oral ketoconazole. Some patients had no obvious risk factors for liver disease. RECORLEV is associated with serious hepatotoxicity. Evaluate liver enzymes prior to and during treatment
2. Recorlev is associated with dose-related QT interval prolongation. QT interval prolongation may result in life threatening ventricular dysrhythmias such as torsades de pointes. Perform ECG prior to and during treatment

Patients with pituitary or adrenal carcinoma were excluded from clinical trials.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Recorlev TABS 150MG

REFERENCES

1. Recorlev (levoketoconazole) tablets, oral [prescribing information]; Chicago, IL: Xeris Pharmaceuticals, Inc, June 2023.
2. Fleseriu, M., Pivonello, R., Elenkova, A., Salvatori, R., Auchus, R. J., Feelders, R. A., Geer, E. B., Greenman, Y., Witek, P., Cohen, F., & Biller, B. (2019). Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial. The lancet. Diabetes & endocrinology, 7(11), 855–865. https://doi.org/10.1016/S2213-8587(19)30313-4
3. Pivonello, R., Elenkova, A., Fleseriu, M., Feelders, R. A., Witek, P., Greenman, Y., Geer, E. B., Perotti, P., Saiegh, L., Cohen, F., & Arnaldi, G. (2021). Levoketoconazole in the Treatment of Patients With Cushing's Syndrome and Diabetes Mellitus: Results From the SONICS Phase 3 Study. Frontiers in endocrinology, 12, 595894. https://doi.org/10.3389/fendo.2021.595894
4. Nieman, L. K., Biller, B. M., Findling, J. W., Murad, M. H., Newell-Price, J., Savage, M. O., Tabarin, A., & Endocrine Society (2015). Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism, 100(8), 2807–2831. https://doi.org/10.1210/jc.2015-1818
5. Fleseriu, M., Auchus, R., Bancos, I., Ben-Shlomo, A., Bertherat, J., Biermasz, N. R., … Biller, B. M. (2021). Consensus on diagnosis and management of Cushing's Disease: A Guideline Update. The Lancet Diabetes & Endocrinology, 9(12), 847–875. doi:10.1016/s2213-8587(21)00235-7

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Contraindications/Exclusions/Discontinuation References	Q3 2025
REVISION- Notable revisions: [include section header in which updates occurred] OR ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review.	Q3 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Other Special Considerations References	Q3 2023
NEW CRITERIA CREATION	Q2 2022