levoketoconazole (Recorlev®)

Policy # 00789
Original Effective Date: 06/13/2022
Current Effective Date: 06/13/2022

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider levoketoconazole (Recorlev®)‡ for the treatment of Cushing's syndrome to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for levoketoconazole (Recorlev) for the treatment of Cushing's syndrome will be considered when the below criteria are met:

- Patient has a diagnosis of endogenous Cushing's syndrome; AND
- Patient is 18 years of age or older; AND
- Patient is not a candidate for pituitary surgery OR surgery has not been curative for the patient; AND
- Patient does not have a diagnosis of pituitary or adrenal carcinoma; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has tried and failed (e.g., intolerance or inadequate response) generic ketoconazole tablets unless there is clinical evidence or patient history that suggests the use of generic ketoconazole tablets will be ineffective or cause an adverse reaction to the patient; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has tried and failed (e.g., intolerance or inadequate response) at least ONE additional alternative treatment for endogenous Cushing's syndrome unless there is clinical evidence or patient history that suggests the alternative treatment options will be ineffective or cause an adverse reaction to the patient. Alternative treatment options for Cushing's syndrome

include pasireotide (Signifor®)‡, generic cabergoline, metyrapone (Metopirone®)‡, or mitotane (Lysodren®)‡.
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of levoketoconazole (Recorlev) for the treatment of patients with a diagnosis of pituitary or adrenal carcinoma or who have not tried and failed BOTH the generic ketoconazole tablets AND at least one additional alternative treatment to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of levoketoconazole (Recorlev) when patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Recorlev contains the active ingredient levoketoconazole which is the 2S, 4R-enantiomer of racemic ketoconazole. It was approved by the Food and Drug Administration (FDA) via the 505(b)(2) pathway relying on safety and efficacy information with racemic ketoconazole to support approval. Recorlev 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. The recommended dose is 150 mg orally twice daily with or without food that may be increased to 1200 mg per day depending on response. Racemic ketoconazole has been used off-label for this indication and is mentioned in the clinical practice guidelines, but its use is limited by hepatotoxicity and drug interactions. It should be noted that Recorlev also has black box warnings and contraindications pertaining to hepatotoxicity and QT prolongation. Additionally, concomitant use of Recorlev with sensitive CYP3A4 or CYP3A4 and P-gp substrate drugs is contraindicated.

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Endogenous Cushing's syndrome is a rare heterogenous disorder that leads to cortisol excess. Patients with Cushing's exhibit a variety of signs and symptoms such as high blood pressure, loss of libido, diabetes, weight gain, acne, moon face, truncal obesity, and slender extremities. Goals of treatment include normalizing the cortisol excess, avoiding and reversing the clinical features, and controlling the disease long term. Medications available that have the ability to inhibit adrenocortical steroidogenesis include ketoconazole, metyrapone (Metopirone), mitotane (Lysodren), and etomidate. Cushing's disease is a subset of Cushing's syndrome caused by an adrenocorticotropic hormone (ACTH)-dependent pituitary adenoma. Treatment options for Cushing's disease include the previously mentioned steroidogenesis inhibitors as well as the pituitary directed agents cabergoline and pasireotide (Signifor).

The 2015 Endocrine Society Guidelines recommend surgery as the first line of therapy for the treatment of endogenous Cushing's syndrome. For patients who cannot undergo surgery or for whom surgery is unsuccessful, there are several medication options. The guidelines note that most medical agents are supported by a low level of evidence, but recommend drugs from three classes for patients who fail surgery: 1) Steroidogenesis inhibitors such as ketoconazole or metyrapone, 2) pituitary drugs such as cabergoline and pasireotide, and 3) the GR-II antagonist, mifepristone. Each of these classes have specific risks and benefits that depend on patient characteristics.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Recorlev was approved in December 2021 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The effectiveness of Recorlev in patients with Cushing's syndrome was evaluated in two studies, Study 1 and Study 2.

Study 1 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. This study enrolled 84 patients with Cushing's syndrome and persistent or recurrent disease despite surgery as well as previously medically treated patients and previously untreated patients. The majority (83%) of these had Cushing's disease. Patients with pituitary or adrenal carcinoma were excluded. Persistence or recurrence of Cushing's syndrome was evidenced by the mean of three 24-hour urine free cortisol (UFC) levels ≥1.5 times the upper limit of normal (normal range: 11 to 138 nmol/day or 4 to 50 micrograms/day). For the 79 patients who underwent dose titration, the mean UFC at study baseline was 785 nmol/day, which corresponds to approximately 6 times the upper limit of normal. In the dose titration and maintenance phase, patients were started on 150 mg of Recorlev orally twice daily. The dose could be titrated in 150-mg increments at 2-week intervals to a maximum of 600 mg twice daily to achieve mean of four 24 hour UFC (mUFC) levels within the normal range. The dose was increased if mUFC was above the upper limit of normal and was reduced based on individual tolerability. Patients who achieved a stable therapeutic dose for 4 weeks and achieved a normal mUFC at the end of the dose titration and maintenance phase were eligible for the randomized withdrawal phase. In the randomized withdrawal phase, 44 patients were randomized in a 1:1 ratio to either continue Recorlev or receive matched placebo for approximately 2 months or until early rescue was necessary. The key secondary efficacy endpoint was the proportion of patients with mUFC normalization, defined as a patient with mUFC at or below the upper limit of normal at the end of randomized withdrawal phase without meeting a requirement for early rescue during the randomized withdrawal phase. Among the 39 patients who had normal mUFC at the randomized withdrawal phase baseline, 21 were randomized to the Recorlev group and 18 to the placebo group. The number and percent of patients who had normal mUFC at the end of the randomized withdrawal phase was 11/21 (52.4%) in the Recorlev group and 1/18 (5.6%) in the placebo group, and the treatment difference (CI) was 46.8% (16.5%, 70.2%).

Study 2 was a multicenter, single-arm, open-label study that consisted of 3 study phases (dose titration, maintenance, and extended evaluation) for a total estimated treatment duration of up to 73 weeks. This study enrolled 94 Cushing's syndrome patients naïve to treatment with Recorlev with persistent or recurrent disease despite surgery, previously medically treated patients, and previously untreated patients. For the majority (95%) of patients, the etiology of Cushing's syndrome was benign pituitary adenoma. Patients with pituitary or adrenal carcinoma were excluded. Persistence or recurrence of Cushing's syndrome was evidenced by the mUFC levels greater than or equal to 1.5 times the upper limit of normal. The mean of the mUFC at baseline was 243 micrograms/day,

which corresponds to approximately 5 times the upper limit of normal. In the dose titration phase, 94 patients received a starting dose of 150 mg Recorlev orally twice daily that was titrated approximately every 2 to 3 weeks if mUFC was above the upper limit of normal to a maximum of 600 mg twice daily. Patients who achieved a therapeutic dose were continued to the maintenance phase. Seventy-seven patients who achieved a therapeutic dose entered the maintenance phase and continued treatment with therapeutic dose of Recorlev for 6 months. The dose of Recorlev was allowed to be decreased for safety or tolerability reasons or increased for loss of efficacy. The primary efficacy endpoint was the proportion of patients with normalization of mUFC at the end of the maintenance phase. Normalization of mUFC was defined as mUFC at or below the upper limit of normal based on central laboratory result without requiring a dose increase during the maintenance phase. At the end of the maintenance phase, 29 of 94 patients (30.9%) met the primary endpoint. It should be noted that 51% of patients discontinued treatment prematurely due to adverse reaction, lack of efficacy, or other reasons. The extended evaluation phase of the study included 60 patients who continued treatment with Recorlev for an additional 6 months.

References

1. Recorlev [package insert]. Xeris Pharmaceuticals, Inc. Chicago, IL. Updated January 2022.
2. Cushing's—Recorlev Prior Authorization Policy. Express Scripts. Updated January 2022.

Policy History

Original Effective Date: 06/13/2022
Current Effective Date: 06/13/2022
05/05/2022 Medical Policy Committee review
05/11/2022 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 05/2023

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.