Recorlev (levoketoconazole)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Cushing's syndrome is a rare hormonal disorder that occurs when the body is exposed to high levels of the hormone cortisol for an extended period of time. Cortisol is produced by the adrenal glands, which are located on top of the kidneys, and is essential for many body functions, including regulating blood sugar levels, reducing inflammation, and aiding in the metabolism of fats, carbohydrates, and proteins.

There are two main types of Cushing's syndrome: exogenous and endogenous. Exogenous Cushing's syndrome is caused by the long-term use of high-dose corticosteroid medications, such as prednisone, to treat conditions such as asthma, rheumatoid arthritis, and lupus. Endogenous Cushing's syndrome is caused by the overproduction of cortisol by the adrenal glands themselves or by a tumor in the pituitary gland or elsewhere in the body.

Symptoms of Cushing's syndrome can be wide-ranging and may include:

- Weight gain, especially in the upper body and around the face (moon face)
- Thin skin that bruises easily and heals poorly
- Muscle weakness and wasting
- High blood pressure
- Insulin resistance or diabetes
- Irregular menstrual periods and decreased libido in women
- Decreased fertility and impotence in

men
- Mood changes, including depression and anxiety
- Fatigue and weakness

Diagnosis of Cushing's syndrome can be challenging because the symptoms can be caused by a variety of other conditions. Initial screening tests may include a 24-hour urine free cortisol test, late-night salivary cortisol test, or midnight plasma cortisol test. If screening tests are abnormal, confirmatory tests such as the dexamethasone suppression test or the corticotropin-releasing hormone (CRH) stimulation test may be performed. An ACTH level can help determine if the Cushing's syndrome is ACTH-dependent or ACTH-independent. Imaging studies, such as a CT scan or MRI, may also be used to identify the location of a tumor.

Treatment for Cushing's syndrome depends on the underlying cause. If the syndrome is caused by the long-term use of corticosteroids, gradually reducing the dosage of the medication can help to alleviate symptoms. If the syndrome is caused by a tumor, surgery may be necessary to remove the tumor or the affected gland. Radiation therapy or medication may also be used to shrink or control the tumor. In cases where surgery is not an option or has been unsuccessful, medications such as ketoconazole, metyrapone, and mitotane can be used to reduce cortisol production.

Recorlev (levoketoconazole) is 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.

- Recorlev (levoketoconazole) is not approved for the treatment of fungal infections.
- The safety and effectiveness of Recorlev (levoketoconazole) for the treatment of fungal infections have not been established.

Definitions

"Adrenal glands" are small organs on top of both kidneys that produce hormones regulating a person's metabolism, immune system, blood pressure, and response to stress.

"Adrenocorticotropic hormone (ACTH)" is a hormone made in the pituitary gland. Adrenocorticotropic hormone acts on the outer part of the adrenal gland to control the release of corticosteroid hormones. ACTH is elevated during times of stress.

"Arrhythmia" is a condition in which the heart beats with an irregular or abnormal rhythm.

"Carcinoma" is a cancer arising in the skin tissue or of the lining of internal organs.

"Endogenous" means having an internal cause or origin.

"Exogenous" means having an external cause or origin.

"QT prolongation" occurs when the heart muscle takes a longer time to contract and relax than usual, often causing fast or erratic heartbeats. QT prolongation may increase the risk of developing abnormal heart rhythms and may lead to sudden cardiac arrest.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Recorlev (levoketoconazole)** medically necessary when **ALL** of the following criteria are met:

1. The requested medication is prescribed by or in consultation with an endocrinologist***; AND***
2. The member is 18 years of age or older***; AND***
3. The member has a confirmed diagnosis of endogenous Cushing's syndrome **AND** recent (within the last 3 months) documentation of **BOTH** of the following:
    a. baseline 24-hour urinary free cortisol (UFC) is provided as evidence of hypercortisolism (normal cortisol range: 11-138 nmol/day or 4-50 mcg/day)***; and***
    b. baseline liver enzyme function test (LFTs)***; AND***
4. The member is not a candidate for pituitary surgery or has undergone pituitary surgery that was not curative***; AND***
5. The member is unable to use, or has tried and failed treatment with Signifor (pasireotide)***; AND***
6. The member does **NOT** have documentation of **ANY** of the following:
    a. pituitary or adrenal carcinoma***; or***
    b. baseline QTcF interval >470 msec, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history)***; or***
    c. cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT >3 times the ULN, 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***; or***
    d. known hypersensitivity to levoketoconazole, ketoconazole, or any component of the formulation***; or***
    e. Recorlev (levoketoconazole) will be used concomitantly with any medication(s) or product(s) that:
        i. cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes (e.g., bosutinib, cisapride, clarithromycin, cobimetinib,

crizotinib, disopyramide, dofetilide, dronedarone, eliglustat (in patients that are poor or intermediate metabolizers of CYP2D6 and in patients taking strong or moderate CYP2D6 inhibitors), ivabradine, methadone, midostaurin, nicardipine, pimozide, quinidine, and ranolazine)***; or***

ii. are sensitive substrates of CYP3A4 or CYP3A4 and P-gP (e.g., alfentanil, avanafil, buspirone, conivaptan, dabigatran etexilate, darifenacin, darunavir, digoxin, ebastine, everolimus, fexofenadine, ibrutinib, lomitapide, lovastatin, lurasidone, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, and vardenafil)***; AND***

7. Recorlev (levoketoconazole) will be dosed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature***; AND***
8. Chart documentation and supporting laboratory test results are provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, Recorlev (levoketoconazole) will be approved for 6 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **ALL** of the following are met:

1. the member still meets the applicable Initial Authorization criteria***; AND***
2. recent chart documentation (within the last 6 months) shows the member has experienced therapeutic response to Recorlev (levoketoconazole) as evidenced by **EITHER**:
    a. Reduction in 24-hour urinary free cortisol (UFC) levels compared to baseline***; or***
    b. Improvement in clinical signs and symptoms of Cushing's syndrome based on the prescriber's assessment (e.g., systolic and diastolic blood pressure, weight, body mass index [BMI], waist circumference)***; AND***
3. The member will continue to be monitored for adverse effects including liver function and QT prolongation while on therapy.

Table 1: Recorlev (levoketoconazole) Recommended Dosage

Indication	Initial dose	Maximum dose	Additional Considerations
endogenous hypercortisolemia in adult patients with	150 mg orally twice daily	1,200 mg per day, given as 600 mg orally twice daily	Titrate the dosage by 150 mg daily, no more frequently than every 2-

Cushing's syndrome			3 weeks based on 24-hour urine free cortisol levels and patient tolerability. The dosage may be reduced to 150 mg once daily if needed for reasons of tolerability

Experimental or Investigational / Not Medically Necessary

Recorlev (levoketoconazole) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Cushing's syndrome secondary to:
  - malignancy (including pituitary or adrenal carcinoma)***; or***
  - non-endogenous source of hypercortisolism, including pharmacological corticosteroids or ACTH***; or***
- the treatment of advanced prostatic carcinoma***; or***
- for treatment of dysfunctional hirsutism***; or***
- for the treatment of fungal infections***; or***
- for treatment of hypercalcemia***; or***
- for treatment of precocious puberty.

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