BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 2/17/2022
LAST REVIEW DATE:
LAST CRITERIA REVISION DATE:
ARCHIVE DATE:

RECORLEV® (levoketoconazole) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy 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 BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

RECORLEV® (levoketoconazole) oral

Criteria:

- **Criteria for initial therapy:** Recorlev (levoketoconazole) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patients' diagnosis or is in consultation with an Endocrinologist

2. Individuals 18 years of age or older

3. A confirmed diagnosis of endogenous hypercortisolemia in Cushing's syndrome where pituitary surgery is not an option or has not been curative

4. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Serum potassium and magnesium with correction if abnormal before starting therapy
    b. Electrocardiogram (ECG)

5. Documented failure, contraindication per FDA label, intolerance to **TWO** of the following:
    a. Oral ketoconazole
    b. Oral cabergoline
    c. Oral Metopirone (metyrapone)
    d. Oral Lysodren (mitotane)

5. Individual does not have a fungal infection

6. Individual is not using chronic glucocorticosteroids

7. There are **NO** FDA-label contraindications, such as:
    a. Cirrhosis
    b. Acute liver disease or poorly controlled chronic liver disease
    c. Baseline AST or ALT > 3 times the upper limit of normal
    d. Recurrent symptomatic cholelithiasis
    e. prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment
    f. Extensive metastatic liver disease
    g. Prolonged QTcF interval > 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or prolonged QT syndrome
    h. Hypersensitivity to levoketoconazole, ketoconazole or any excipient
    i. Taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes (See definitions section)
    j. Taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gp substrates (See definitions section)

8. Individual is not on either a CYP3A4 inhibitor or CYP3A4 inducer (See definitions section)

9. There are no significant interacting drugs

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Recorlev (levoketoconazole) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist

2. Individual's condition responded while on therapy
    a. Response is defined as:
        i. Achieved and maintains **THREE** of the following:
            1. A urinary free cortisol (UFC) less than or equal to the upper limit of normal (ULN)
            2. Cortisol levels is within normal limits
            3. A reduction in Cushing's syndrome manifestations of cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight
            4. No evidence of disease progression

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Significant or recurrent elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin
        ii. First episode or recurrent QTc prolongation greater than 500 msec
        iii. Severe hypocortisolism
        iv. Adrenal insufficiency

5. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-cancer Medications**

2. **Off-Label Use of Cancer Medications**

RECORLEV® (levoketoconazole) oral

Description:

Recorlev (levoketoconazole), a cortisol synthesis inhibitor, is indicated for the treatment of endogenous hypercortisolemia in Cushing's syndrome where pituitary surgery is not an option or has not been curative.

Cushing's syndrome, also known as hypercortisolism, is an uncommon disorder that occurs because of excess cortisol. It can come from chronic use of corticosteroid medications or tumor of the pituitary or adrenal glands producing too much cortisol. Cushing's disease is a specific type of Cushing syndrome caused by a benign tumor located in the pituitary gland that secretes too much adrenocorticotropic hormone (ACTH), which in turn increases cortisol.

Exogenous Cushing syndrome is most commonly due to chronic use of glucocorticoid medications that cause iatrogenic Cushing's syndrome. Endogenous Cushing syndrome is most often caused by hormone-secreting tumors of the adrenal glands or the pituitary.

In vitro, levoketoconazole inhibits key steps in the synthesis of cortisol and testosterone, principally those mediated by CYP11B1 (11β hydroxylase), CYP11A1 (the cholesterol side-chain cleavage enzyme, the first step in the conversion of cholesterol to pregnenolone), and CYP17A1 (17α-hydroxylase).

Ketoconazole tablets contain equal parts levoketoconazole and dextroketoconazole in a racemic mixture, Levoketoconazole is the 2S, 4R enantiomer of ketoconazole.

Definitions:

Some Package Label Interactions: [Note: not a complete list]

CYP3A4 or CYP3A4 and P-gp Substrates That May Prolong QT

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

Sensitive CYP3A4 or CYP3A4 and P-gp Substrates

Alfentanil, avanafil, buspirone, conivaptan, dabigatran etexilate, darifenacin, darunavir, digoxin, ebastine, everolimus, fexofenadine, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, and vardenafil

Strong CYP3A4 Inhibitors

Antivirals (e.g., ritonavir, ritonavir-boosted darunavir, ritonavir boosted fosamprenavir, saquinavir)
Glucocorticoid and progesterone receptor antagonists (e.g., mifepristone)
Others clarithromycin, conivaptan, tipranavir

Strong CYP3A4 Inducers

Antibacterials (e.g., isoniazid, rifabutin, rifampicin), Anticonvulsants (e.g., carbamazepine, phenytoin), Antivirals (e.g., efavirenz, nevirapine), Cytotoxic agents (e.g., mitotane)

RECORLEV® (levoketoconazole) oral

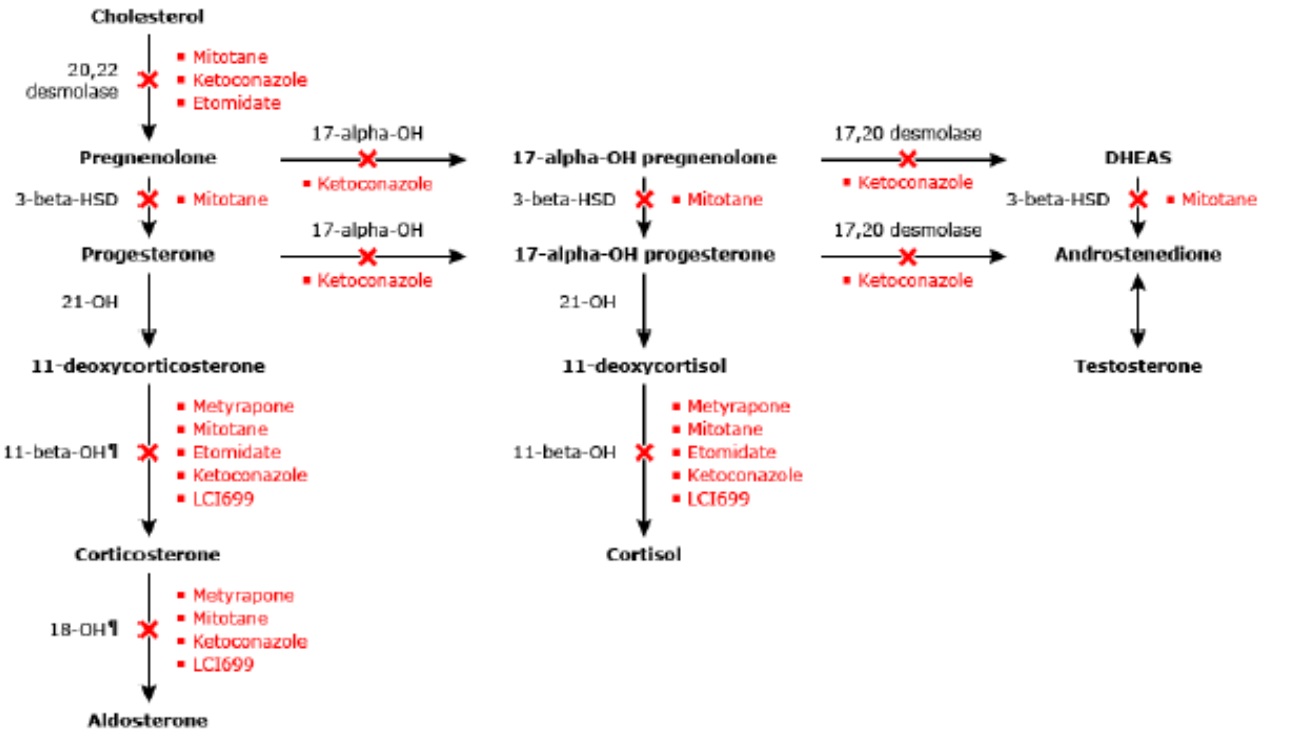
Gastric Acid Suppressors
Avoid use of H2- receptor antagonists and proton pump inhibitors

Sucralfate
Avoid use

Signs and symptoms of Cushing's syndrome	
More Common	**Less Common**
Decreased libido	ECG abnormalities or atherosclerosis
Obesity/weight gain	Striae
Plethora	Edema
Round face	Proximal muscle weakness
Menstrual changes	Osteopenia or fracture
Hirsutism	Headache
Hypertension	Backache
Ecchymoses	Recurrent infections
Lethargy, depression	Abdominal pain
Dorsal fat pad	Acne
Abnormal glucose tolerance	Female balding

RECORLEV® (levoketoconazole) oral

Steroidogenesis in adrenal cortex affected by specific enzyme inhibitors*



Steroidogenesis in the adrenal cortex denoting the specific pathways inhibited by ketoconazole (KTZ), metyrapone (MTR), mitotane, etomidate, and newer steroidogenesis inhibitors.

17-alpha-OH: 17-alpha-hydroxylase; DHEAS: dehydroepiandrosterone sulfate; 3-beta-HSD: 3-beta-hydroxysteroid dehydrogenase; 21-OH: 21-hydroxylase; 11-beta-OH: 11-beta-hydroxylase; LCI699: osilodrostat; 18-OH: 18-hydroxylase.
* Refer to UpToDate table for nomenclature used for steroidogenic enzymes.
¶ Aldosterone synthase.

Resources:

Recorlev (levoketoconazole) product information, revised by Xeris Pharmaceuticals, Inc. 01-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 31, 2022.

Nieman LK. Epidemiology and clinical manifestations of Cushing's syndrome. In: UpToDate, Lacroix A, Martin KA (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 05, 2021. Accessed February 06, 2022.

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Nieman LK. Establishing the cause of Cushing's syndrome. In: UpToDate, Lacroix A, Martin KA (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 30, 2021. Accessed February 06, 2022.

Nieman LK. Establishing the diagnosis of Cushing's syndrome. In: UpToDate, Lacroix A, Martin KA (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated May 29, 2021. Accessed February 06, 2022.

Nieman LK. Overview of the treatment of Cushing' syndrome. In: UpToDate, Lacroix A, Martin KA (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated November 30, 2021. Accessed February 06, 2022.

Nieman LK. Medical therapy for hypercortisolism (Cushing's syndrome). In: UpToDate, Lacroix A, Martin KA (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 06, 2021. Accessed February 06, 2022.