BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

**PHARMACY COVERAGE GUIDELINE**

# KORLYM™ (mifepristone) oral tablet

**This Pharmacy Coverage Guideline (PCG):**
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

**Scope**
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

**Instructions & Guidance**
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

## Criteria:

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

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

  2. Individual is 18 years of age or older.

  3. Individual has a confirmed diagnosis of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who has type 2 diabetes mellitus or glucose intolerance.

  4. Individual has failed surgery **OR** is not a candidate for surgery.



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5. Hypercortisolism is not due to use of corticosteroids.

6. Individual has poorly controlled diabetes mellitus (HgA1c > 8%) or glucose elevation is being treated with anti-diabetic therapy.

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

8. The individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Negative pregnancy test in a woman of childbearing potential, if treatment with Korlym is interrupted for more than 14 days another negative pregnancy test is needed
    b. Serum potassium to correct any hypokalemia prior to initiation of treatment

9. There are **NO** FDA-label contraindications, such as:
    a. Pregnancy
    b. Woman with a history of unexplained vaginal bleeding
    c. Woman with endometrial hyperplasia with atypia or endometrial carcinoma
    d. Concurrent use with CYP3A metabolized drugs (such as simvastatin or lovastatin) and CYP3A substrates with narrow therapeutic ranges (such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus)
    e. Concurrent use with systemic corticosteroid for a medical condition where such use is lifesaving (such as immunosuppression in organ transplantation)

10. Will not be used in a patient with severe hepatic impairment (Child-Pugh Class C).

11. Will not be used with drugs known to cause QT interval prolongation or in an individual with potassium channel variants that result in a long QT interval.

12. Will not be used with carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, and St. John's Wort.

13. Woman patient of childbearing potential is using non-hormonal contraception during and for 1 month after therapy.

**Initial approval duration**: 2 months

- **Criteria for continuation of coverage (renewal request):** Korlym (mifepristone) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

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



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2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
    a. Achieved and maintains at least a 25% reduction in glucose from baseline
    b. Achieved and maintains at least a 2% reduction in HgA1c from baseline
    c. Achieved and maintains a reduction in Cushing's syndrome manifestations of cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight

3. Individual has been adherent with the medication.

4. Individual continues to treat diabetes mellitus or glucose elevation with anti-diabetic therapy.

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Adrenal insufficiency
        ii. Severe or uncorrectable hypokalemia

6. Woman patient of childbearing potential is using non-hormonal contraception during and for 1 month after therapy.

7. Will not be used in a patient with severe hepatic impairment (Child-Pugh Class C).

8. Will not be used with drugs known to cause QT interval prolongation or in an individual with potassium channel variants that result in a long QT interval.

9. Will not be used with carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, and St. John's Wort.

10. Woman patient of childbearing potential is using non-hormonal contraception during and for 1 month after therapy.

**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**

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**Description:**

Korlym (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and who have failed surgery or are not candidates for surgery. Korlym should not be used in the treatment of patients with type 2 diabetes unless it is secondary to Cushing's syndrome.



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Korlym (mifepristone) acts as an antagonist at the progesterone receptor (PR), glucocorticoid receptor type II (GR-II), and androgen receptor (AR). It does not bind to either the estrogen receptor (ER) or mineralocorticoid receptor (MR). Antagonism of the progesterone receptors occurs at low doses whereas antagonism of the glucocorticoid receptors occurs at higher doses. Mifepristone inhibits the actions of exogenous and endogenous glucocorticoids and progestins.

Cortisol is secreted by the cortex of the adrenal glands in response to the pituitary hormone adrenocorticotropic hormone (ACTH). ACTH is secreted in response to corticotropin releasing hormone (CRH) from the hypothalamus. Under normal conditions, pituitary ACTH secretion is inhibited by increasing levels of Cortisol through negative feedback regulation on CRH in the hypothalamus and ACTH in the pituitary.

Mifepristone inhibits the central actions of Cortisol by preventing its negative feedback on ACTH and CRH secretion through antagonism of central GR-II, and it inhibits peripheral actions by inhibiting Cortisol's effects on protein and glucose metabolism. Its actions affect the HPA axis in such a way as to increase circulating Cortisol levels yet at the same time block the effects of Cortisol. The mineralocorticoid effects of excess Cortisol are not inhibited. In addition to increases in Cortisol, administration causes elevations in TSH, androstenedione, estrone, testosterone and estradiol.

Cushing's syndrome is a multisystem disorder defined as the set of clinical abnormalities resulting from chronic high levels of Cortisol regardless of the cause for the elevation of Cortisol. It can be due to either long-term use of glucocorticoid medication, or diseases that result in excess Cortisol, ACTH, or CRH release. When the cause of Cushing's syndrome is found to be from excessive use of glucocorticoid drugs it may be referred to as exogenous Cushing's syndrome. Cushing's disease is a type of Cushing's syndrome that results from excessive pituitary production of ACTH usually due to a pituitary adenoma that produces large amounts of ACTH that causes the adrenal glands to produce excessive levels of Cortisol.

Manifestations of Cushing's syndrome may include cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, abnormal glucose tolerance, hypertension, and excess total body weight.

Treatment of Cushing's disease includes surgical removal of the source of ACTH secretion. Radiotherapy is utilized in patients with a recurrence after surgery. In patients who fail surgery and/or radiotherapy, medical management is recommended prior to bilateral adrenalectomy. Medical management includes use of Ketoconazole or Mitotane.

Mifepristone, the active ingredient of Korlym, is also found in Mifeprex. When used with the prostaglandin analogue Cytotec® (misoprostole), Mifeprex has the FDA labeled indication for termination of pregnancy. Mifeprex is available only through a restricted distribution program limited to specialty clinics, medical offices, and hospitals, and can only be prescribed by medical providers who have enrolled in a certification program. In addition, patients must be enrolled and must provide a copy of their signed agreement before receiving Mifeprex. FDA does not require a restricted distribution for Korlym. The manufacturer has voluntarily proposed distributing Korlym through a central pharmacy using the Support Program for Access and Reimbursement for Korlym (SPARK).



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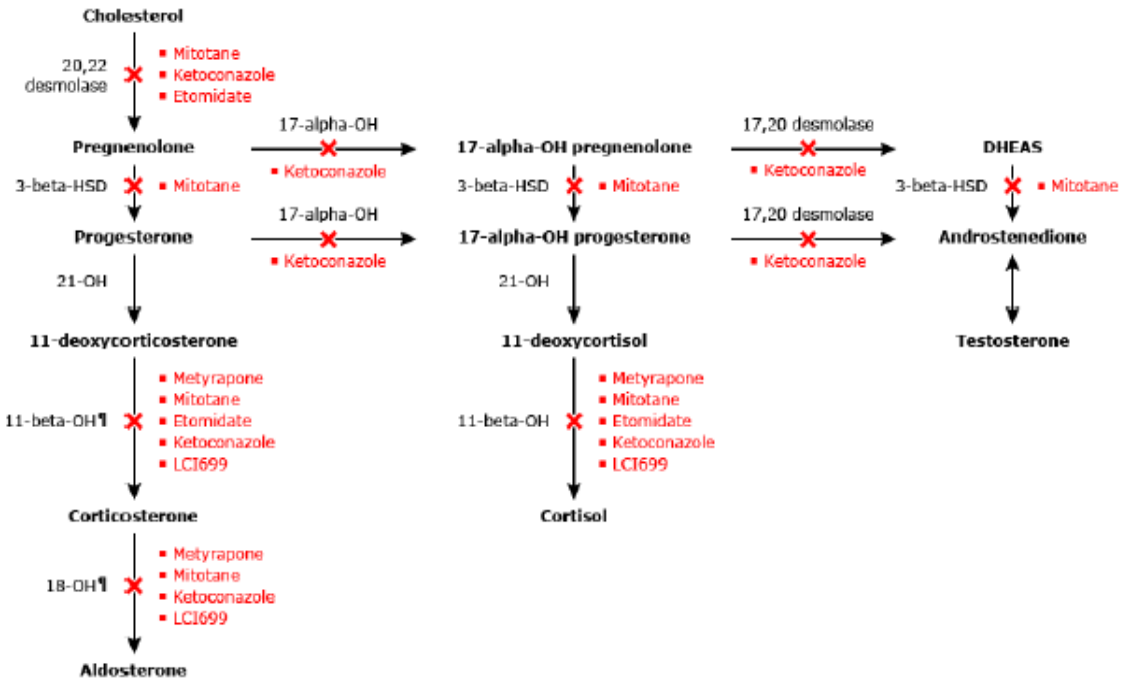
## Definitions:

| 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 |

**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.



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**The Child-Pugh classification system:**

| | Score: 1 point | Score: 2 points | Score: 3 points |
|---|---|---|---|
| **Serum Albumin** (g/dL) | >3.5 | 3.0 - 3.5 | <3.0 |
| **Serum Bilirubin** (mg/dL) | <2.0 | 2.0 - 3.0 | >3.0 |
| **Prothrombin time** (seconds) | 1 - 4 | 4 - 6 | >6 |
| **Ascites** | none | moderate | severe |
| **Encephalopathy** | none | mild | severe |

The three classes and their scores are:

- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score >9: Decompensated disease

## Resources:

Korlym (mifepristone) product information, revised by Corcept Therapeutics 11-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 26, 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 on April 05, 2021. Accessed July 26, 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 on May 29, 2020. Accessed July 26, 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 on November 30, 2021. Accessed July 26, 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 on June 24, 2022. Accessed July 26, 2022.



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