BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

KORLYM™ (mifepristone) oral
Mifepristone oral

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 prior authorization 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) or generic 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 an individual 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

5. Hypercortisolism is **not** due to chronic use of corticosteroids

6. Individual has poorly controlled diabetes mellitus or glucose elevation despite treatment with anti-diabetic therapy

7. Use of requested agent **is not** for the treatment of type 2 diabetes mellitus that is not related to endogenous Cushing's syndrome

8. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **TWO** of the following agents:
    a. Ketoconazole monotherapy
    b. Metopirone (metyrapone) monotherapy
    c. Ketoconazole with metyrapone

9. **For brand Korlym**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic mifepristone** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

10. 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, with correction of any hypokalemia prior to initiation of treatment

11. 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 corticosteroid use is lifesaving (such as immunosuppression in organ transplantation or an autoimmune disorder)

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

13. 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

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

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

Initial approval duration: 2 months

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- **Criteria for continuation of coverage (renewal request):** Korlym (mifepristone) or generic 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

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. **For brand Korlym**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic mifepristone** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

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

6. 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
        iii. Severe QT interval prolongation

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

8. Use of requested agent **is not** for the treatment of type 2 diabetes mellitus that is not related to endogenous Cushing's syndrome

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

10. 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

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

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

Renewal duration: 12 months

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- 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**

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.

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.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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

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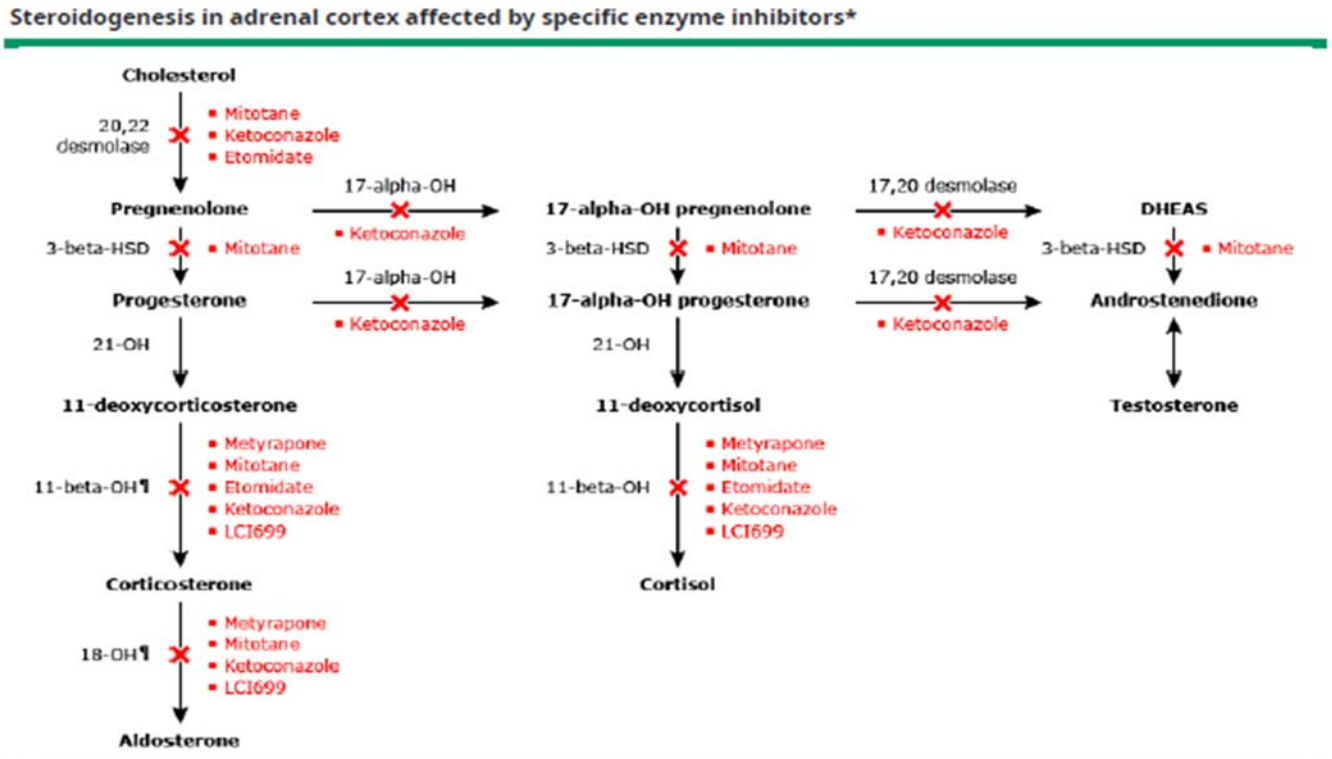

Steroidogenesis in the adrenal cortex denoting the specific pathways inhibited by ketoconazole (KTZ), metyrapone (MTR), mitotane, etomidate, and newer steroidogenesis inhibitors.

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.

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 May 31, 2024.

Mifepristone product information, revised by Actavis Pharma, Inc. 02-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 10, 2024.

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Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100(8):2807-2831. Accessed June 23, 2020. Re-evaluated July 11, 2024.