



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 2/15/2013
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

KORLYM™ (mifepristone) oral tablet

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.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

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.**



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 2/15/2013
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

KORLYM™ (mifepristone) oral tablet

Criteria:

- **Criteria for initial therapy:** Korlym (mifepristone) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist
 2. Individuals 18 years of age or older
 3. A confirmed diagnosis of hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who have 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 use of corticosteroids
 6. Individuals with poorly controlled diabetes mellitus (H_gA_{1c} > 8%) or glucose elevation is being treated with anti-diabetic therapy
 7. Individual has failure, intolerance, or contraindication to **TWO** of the following agents:
 - a. Oral ketoconazole
 - b. Oral cabergoline
 - c. Oral Metopirone (metyrapone)
 - d. Oral Lysodren (mitotane)
 8. **ALL** of the following baseline testing have been completed before initiation of treatment:
 - a. Negative pregnancy test in a woman of child bearing 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 CYP 3A metabolized drugs (such as simvastatin or lovastatin) and CYP 3A substrates with narrow therapeutic ranges (such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus)
 - e. Concurrent use with a long-term corticosteroid used for a medical condition where such use is lifesaving (such as immunosuppression in organ transplantation)
 - f. Concurrent use with cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus
 - g. Prior hypersensitivity reaction to mifepristone or to any components of the product
 10. Will not be used in a patient with severe hepatic impairment (Child-Pugh Class C)



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 2/15/2013
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

KORLYM™ (mifepristone) oral tablet

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, rifapentin, and St. John's Wort
13. Woman patient of child bearing 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** 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 an Endocrinologist
2. Individual's condition responded while on therapy
 - a. Response is defined as **TWO** of the following:
 - i. Achieved and maintains at least a 25% reduction in glucose from baseline
 - ii. Achieved and maintains at least a 2% reduction in HgA1c from baseline
 - iii. 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
 - 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 child bearing potential is using non-hormonal contraception during and for 1 month after therapy
7. There are no significant interacting drugs

Renewal duration: 12 months



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 2/15/2013
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

KORLYM™ (mifepristone) oral tablet

- 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 a Non-cancer Medications**
 2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**
-

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.



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 2/15/2013
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

KORLYM™ (mifepristone) oral tablet

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.

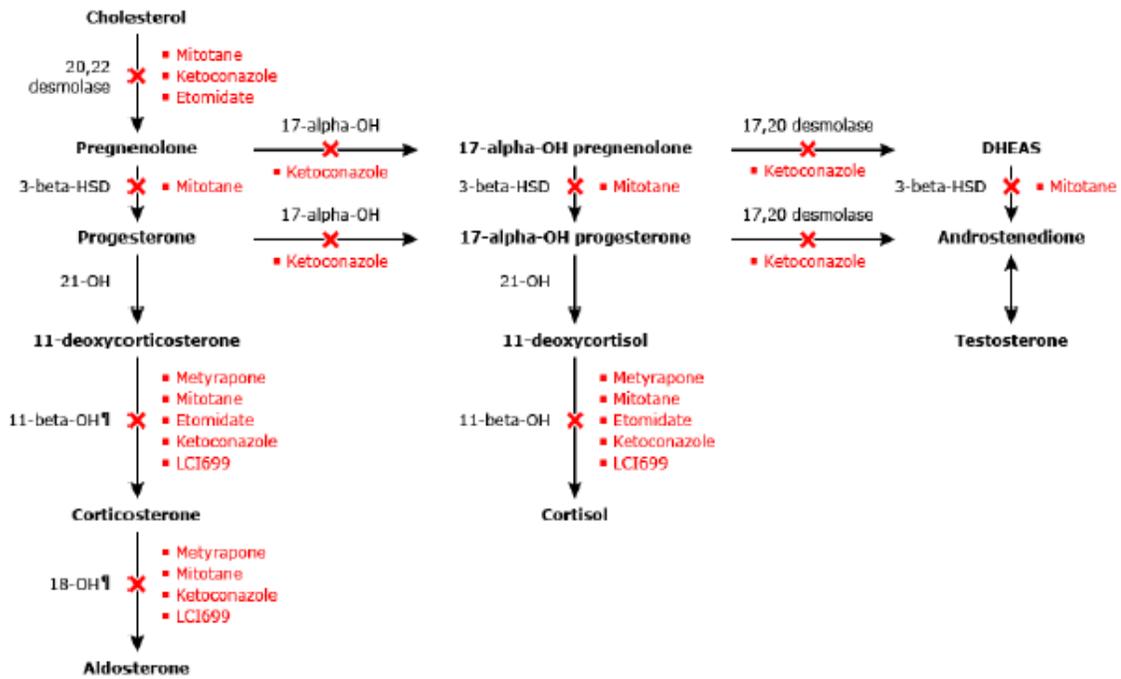
Mifepristone, the active ingredient of Korlym, is also found in Mifeprex. When used with the prostaglandin analogue Cytotec® (misoprostole), Mifeprex has the FDA labeled indication for termination of pregnancy. Mifeprex is available only through a restricted distribution program limited to specialty 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).

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

KORLYM™ (mifepristone) oral tablet

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.

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



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 2/15/2013
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

KORLYM™ (mifepristone) oral tablet

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 on July 22, 2021.

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>. Accessed on July 22, 2021.

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>. Accessed on July 22, 2021.

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>. Accessed on July 22, 2021.

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>. Accessed on July 22, 2021.
