BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 2/15/13**
SECTION: DRUGS	**LAST REVIEW DATE: 8/02/18**
	LAST CRITERIA REVISION DATE: 8/02/18
	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.

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.**

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Criteria:

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

1. Individuals 18 years of age or older
2. A confirmed diagnosis of hyperglycemia secondary to hypercortisolism in individual with endogenous Cushing's syndrome
3. Individual has type 2 diabetes mellitus **OR** glucose intolerance from endogenous Cushing's syndrome
4. Individual has failed surgery **OR** is not a candidate for surgery
5. Hypercortisolism is not due to use of corticosteroids
6. Treatment of individuals with poorly controlled diabetes mellitus (HgA1C > 8%) or glucose elevation is being treated with anti-diabetic therapy
7. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use **TWO** the following preferred step therapy agents:
   - Oral ketoconazole
   - Oral cabergoline
   - Oral Metopirone (metyrapone)
   - Oral Lysodren (mitotane)
8. **ALL** of the following baseline testing have been completed before initiation of treatment:
   - 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
   - Serum potassium to correct any hypokalemia prior to initiation of treatment
9. There are **NO** contraindications:
   - Contraindications include:
     - Pregnancy
     - Woman with a history of unexplained vaginal bleeding
     - Woman with endometrial hyperplasia with atypia or endometrial carcinoma
     - Concurrent use with simvastatin or lovastatin
     - Concurrent use with a long-term corticosteroid used for a medical condition where such use is life-saving (such as immunosuppression in organ transplantation)
     - Concurrent use with cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus
     - 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)
11. Will not be used with drugs known to cause QT interval prolongation

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

13. Woman patient of child bearing potential should use non-hormonal contraception during and for 1 months after therapy

14. Woman patient who is breast feeding an infant or child should stop breast feeding during 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's condition responded while on therapy
    - Response is defined as **ALL** of the following:
        - Achieved and maintains at least a 25% reduction in glucose from baseline
        - Achieved and maintains at least a 2% reduction in HgA1C from baseline
        - Achieved and maintains a reduction in Cushing's syndrome manifestations of cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight

2. Individual has been adherent with the medication

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

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Adrenal insufficiency
        - Severe or uncorrectable hypokalemia

5. There are no significant interacting drugs

Renewal duration: 12 months

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

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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:

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 package insert. Revised by manufacturer on 10-2016. Reviewed on 06-27-2017

Korlym package insert. Revised by manufacturer on June 2013 reviewed on 06-14-2015

Korlym. Package Insert, reference ID: 3089791, issued: 02/2012. Reviewed on October 13, 2012

MICROMEDEX® accessed October 13, 2012.

J Clin Endocrinol Metab July 2008; 93(7):2454-2462: Treatment of Adrenocorticotropiin-dependent Cushing' Syndrome: A concensus statement.

FDA Center for Drug Evaluation and Research 2012 Pharmacologic review(s): Korlym.

Korlym package insert. Revised by manufacturer on 05-2017. Reviewed on 07-09-2018

UpToDate: Establishing the diagnosis of Cushing's syndrome. Current through Jun 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/establishing-the-diagnosis-of-cushings-syndrome?search=cushings%20diagnosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

UpToDate: Medical therapy of hypercortisolism (Cushing's syndrome). Current through Jun 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/medical-therapy-of-hypercortisolism-cushings-

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syndrome?search=hyperglycemia%20secondary%20to%20hypercortisolism%20with%20endogenous%20Cushing's%20syndrome&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

UpToDate: Overview of the treatment of Cushing's syndrome. Current through Jun 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-the-treatment-of-cushings-syndrome?search=hyperglycemia%20secondary%20to%20hypercortisolism%20with%20endogenous%20Cushing's%20syndrome&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

UpToDate: Establishing the cause of Cushing's syndrome. Current through Jun 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/establishing-the-cause-of-cushings-syndrome?search=cushings%20diagnosis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

UpToDate: Epidemiology and clinical manifestations of Cushing's syndrome. Current through Jun 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/epidemiology-and-clinical-manifestations-of-cushings-syndrome?search=cushings%20diagnosis&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.