



Louisiana

mifepristone (Korlym[®])

Policy # 00383

Original Effective Date: 08/21/2013

Current Effective Date: 10/17/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of mifepristone (Korlym[®])[†] for use in patients with endogenous Cushing's syndrome to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for mifepristone (Korlym) will be considered when all of the following criteria are met:

- Initial request (6 months)
 - Patient has a diagnosis of hyperglycemia secondary to endogenous Cushing's Syndrome; AND
 - Patient is 18 years of age or older; AND
 - Patient has failed surgery OR is not a candidate for surgery; AND
 - Patient has a diagnosis of type 2 diabetes mellitus OR glucose intolerance/insulin resistance with a documented hemoglobin A1c; AND
 - The patient has had an adequate trial (Note: at least 3 months followed by hemoglobin A1c test) and failure (defined as lack of improvement in hemoglobin A1c) of at least ONE conventional anti-hyperglycemic agent (e.g. metformin, sulfonylurea, insulin), unless there is clinical evidence or patient history that suggests the use of the alternative products will be ineffective or cause an adverse reaction to the patient; AND
 - The patient has had a trial and failure or inability to tolerate at least ONE of the steroidogenesis inhibitors [generic ketoconazole, metyrapone (Metopirone^{®†}), or mitotane (Lysodren^{®†})] unless there is clinical evidence or patient history that suggests the use of the alternative products will be ineffective or cause an adverse reaction to the patient; AND
 - If the patient has Cushing's Disease, patient has failed or is unable to tolerate at least ONE of the pituitary directed agents [generic cabergoline or pasireotide (Signifor^{®†})], unless there is clinical evidence or patient history that suggests the use of the alternative products will be ineffective or cause an adverse reaction to the patient.
- Continuation request (1 years)
 - Member continues to meet criteria for initial approval; AND
 - Member has documented improvement in hyperglycemia based on hemoglobin A1c.

*(Note: This specific patient criterion is an additional Company requirement and will be denied as not medically necessary** if not met.)*

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*(Note: The specific patient criteria requiring the patient to try and fail additional medications are additional Company requirements and will be denied as not medically necessary** if not met)*

When Services are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Korlym without evidence that the patient has had an improvement in hemoglobin A1c with the drug or has had an adequate trial and failure of an anti-hyperglycemic agent, a steroidogenesis inhibitor, and a pituitary directed agent (where applicable) to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of mifepristone (Korlym) when patient selection criteria are not met (with the exception of those considered to be **not medically necessary****) to be **investigational**.*

Background/Overview

Korlym is a cortisol receptor blocker that is approved to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Korlym is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses. Korlym has high affinity for the GR-II receptor but little affinity for the GR-1 (mineralocorticoid) receptor. Each tablet contains 300mg of active ingredient. The recommended starting dose is 300mg once daily with a meal. Based on clinical response and tolerability, the dose may be increased in 300mg increments to a maximum of 1200mg once daily. There are also dosage adjustments for renal and hepatic impairment.

Endogenous Cushing's Syndrome

Endogenous Cushing's syndrome is a rare heterogeneous disorder that leads to cortisol excess. Patients with Cushing's exhibit a variety of signs and symptoms such as high blood pressure, loss of libido, diabetes, weight gain, acne, moon face, truncal obesity, and slender extremities. Goals of treatment include normalizing the cortisol excess, avoiding and reversing the clinical features, and controlling the disease long term. Medications available that have the ability to inhibit adrenocortical steroidogenesis include ketoconazole (Nizoral), metyrapone (Metopirone), mitotane (Lysodren), and etomidate (Amidate). Cushing's Disease is a subset of Cushing's syndrome caused by an adrenocorticotrophic hormone (ACTH)-dependent pituitary adenoma. Treatment options for Cushing's Disease include the previously mentioned steroidogenesis inhibitors as well as the pituitary directed agents cabergoline (Dostinex) and pasireotide (Signifor).

The 2015 Endocrine Society Guidelines recommend surgery as the first line of therapy for the treatment of Endogenous Cushing's syndrome. For the patients who cannot undergo surgery or for whom surgery is

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unsuccessful, there are several medication options. The guidelines note that most medical agents are supported by a low level of evidence, but recommend drugs from three classes for patients who fail surgery: 1) Steroidogenesis inhibitors such as ketoconazole (Nizoral) or Metopirone (metyrapone), 2) Pituitary drugs such as cabergoline (Dostinex) and Signifor (pasireotide), and 3) the GR-II antagonist, Korlym (mifepristone). Each of these classes have specific risks and benefits that depend on patient characteristics.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Korlym was approved in February of 2012 to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Korlym carries a boxed warning for termination of pregnancy. Korlym has antiprogesterational effects and will result in the termination of pregnancy.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Korlym was assessed in an uncontrolled, open label trial in patients with evidence of hypercortisolemia despite poor surgical treatment and radiotherapy. There was a diabetes cohort and a hypertension cohort in this study. Treatment with Korlym was started at 300mg once daily and dosages were increased to maximum doses of 900-1200mg per day based on their weight, clinical tolerance, and clinical response. The primary efficacy endpoint for the diabetes cohort was an analysis of responders. A responder was defined as a patient who had a $\geq 25\%$ reduction in glucose area under the curve (AUC). In this study, 60% of the patients (15 of 25) in the diabetes cohort were treatment responders. The median decrease in glucose AUC was 35%. The baseline hemoglobinA1c was 7.43 in the diabetes cohort at baseline and decreased to 6.29 at week 24. Fasting plasma glucose was reduced from 149mg/dL to 104mg/dL. Antidiabetic medications were reduced in 7 of the 15 patients taking antidiabetic medications at baseline.

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Policy History

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| 08/01/2013 | Medical Policy Committee review |
| 08/21/2013 | Medical Policy Implementation Committee approval. New policy. |
| 08/07/2014 | Medical Policy Committee review |
| 08/20/2014 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/06/2015 | Medical Policy Committee review |
| 08/19/2015 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/04/2016 | Medical Policy Committee review |
| 08/17/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/03/2017 | Medical Policy Committee review |
| 08/23/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 10/05/2017 | Medical Policy Committee review |
| 10/18/2017 | Medical Policy Implementation Committee approval. Added a requirement for patients to try and fail an anti-hyperglycemic medication and at least one other agent for the treatment of Cushing's syndrome prior to getting Korlym. Added criteria for re-approval after 6 months of therapy and updated the background information to reflect the guidelines. |
| 10/04/2018 | Medical Policy Committee review |
| 10/17/2018 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
- Next Scheduled Review Date: 10/2019

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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