Original Effective Date: 05/01/2017
Current Effective Date: 09/01/2024
Last P&T Approval/Version: 07/31/2024
Next Review Due By: 07/2025
Policy Number: C10881-A

Korlym (mifepristone)

PRODUCTS AFFECTED

Korlym (mifepristone), mifepristone

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This 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 Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Endogenous Cushing's Syndrome (CS)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. ENDOGENOUS CUSHING'S SYNDROME:
1. Diagnosis of ENDOGENOUS Cushing's Syndrome
   AND

2. Documentation of a diagnosis of type 2 diabetes mellitus or glucose intolerance secondary to Cushing's syndrome [DOCUMENTATION REQUIRED assessed by: Fasting serum glucose test, oral glucose tolerance test, or Hemoglobin A1c test (HbA1c)]
   AND
3. Females of Reproductive Potential: Prescriber attests to exclusion of pregnancy prior to request, if treatment is interrupted for more than 14 days, and member has been counseled on use of non-hormonal medically acceptable methods of contraception while on treatment with Korlym (mifepristone)
   AND
4. Documentation of trial and failure, or labeled contraindication to Steroidogenesis inhibitor such as: ketoconazole tablets, Metopirone (metyrapone capsules), Lysodren (mitotane tablets), OR pituitary directed: cabergoline, or Signifor (pasireotide) to normalize cortisol levels for the treatment of Cushing's syndrome
   AND
5. Documentation that surgery has not been curative or member is not a candidate for surgery
   AND
6. Prescriber attests that member has a normal potassium level (labeled Product Warning to correct hypokalemia prior to therapy)
   AND
7. Prescriber attest to (or the clinical review has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Korlym (mifepristone) include: pregnancy, concurrently taking CYP3A metabolized drugs (such as simvastatin, lovastatin) or CYP3A4 substrates with narrow therapeutic ranges (such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), receiving systemic corticosteroids for lifesaving purposes (e.g., immunosuppression after organ transplantation), women with a history of unexplained vaginal bleeding or with endometrial hyperplasia with atypia or endometrial carcinoma, known hypersensitivity to mifepristone or to any of the product components, do not use with hormonal contraceptives, avoid use with QT interval-prolonging drugs, or in patients with potassium channel variants resulting in a long QT interval]

CONTINUATION OF THERAPY:

A. ENDOGENOUS CUSHING'S SYNDROME:

1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
   AND
2. Documentation of improvement in, or stabilization of, glucose tolerance (or improved glycemic control) as assessed by: Fasting serum glucose test, oral glucose tolerance test, or Hemoglobin A1c test (HbA1c) or Decrease in anti-hyperglycemic medication doses or number of medications [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
4. Prescriber attests a recent review of member's current medication has been completed and there is no concomitant use of CYP3A4 metabolized drugs (such as simvastatin, lovastatin) or CYP3A4 substrates with narrow therapeutic ranges (such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), lifesaving systemic corticosteroids (e.g., immunosuppression after organ transplantation) (a contraindication), or hormonal contraceptives
   AND
5. Females of Reproductive Potential: Prescriber attests to exclusion of pregnancy if treatment is interrupted for more than 14 days, and member has been counseled on use of non-hormonal medically acceptable methods of contraception while on treatment with Korylm (mifepristone)

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified endocrinologist or a physician who specializes in the treatment of Cushing's syndrome. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
300mg – 1200mg daily
Maximum Quantity Limits – 20mg/kg/day

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Progesterone Receptor Antagonists

FDA-APPROVED USES:
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 have failed surgery or are not candidates for surgery
Limitations of Use: Korlym should not be used in the treatment of patients with type 2 diabetes unrelated to endogenous Cushing's syndrome

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Cushing's disease (CD), or pituitary-dependent Cushing's syndrome (CS), is a severe endocrine disease caused by a corticotroph pituitary tumor and associated with increased morbidity and mortality. CD is the most common cause of endogenous CS. The goal of treatment is to rapidly control cortisol excess and achieve long-term remission, to reverse the clinical features and reduce long-term complications associated with increased mortality. (Cuevas-Ramos et al.) Endogenous CS is a serious, debilitating and rare multisystem disorder. It is caused by the overproduction of cortisol (a steroid hormone that increases blood sugar levels) by the adrenal glands. CS occurs in about 20,000 people in the United States, mostly women between the ages of 20 and 50.

Korlym (mifepristone) is the first agent the FDA has approved for the management of CS. Prior to the FDA approval of Korlym (mifepristone), there were no approved medical therapies for the treatment of endogenous CS (high circulating cortisol levels caused by pituitary and adrenal tumors).

Korlym is approved for use in patients with endogenous Cushing's syndrome who have: •Type 2 diabetes or glucose intolerance secondary to hypercortisolism and •Failed surgery or are not candidates for surgery Because hypercortisolism often leads to hyperglycemia in patients with CS, the pivotal trial for Korlym was designed to measure changes in glucose levels in patients with glucose intolerance or type 2 diabetes mellitus.

The treatment of choice in endogenous Cushing syndrome, which is most commonly caused by a corticotroph pituitary adenoma, is surgical removal of the adenoma. Second-line therapies include medical therapy, bilateral adrenalectomy, and radiation therapy. The therapy must be individualized and targeted at normalization of hormone excess, long-term disease control, and reversal of comorbidities caused by the underlying pathology. In patients in whom surgery has failed, medical therapies are considered palliative and are focused on modifying the hypothalamic/pituitary index, activity of the adrenal gland, and activity of the glucocorticoid receptor. Pharmacological agents currently used in the treatment of CD are classified according to their mechanism of action as adrenal steroidogenesis inhibitors, pituitary-directed drugs and glucocorticoid receptor antagonists: (Cuevas-Ramos D et al. 2014)

- Adrenal-blocking (to reduce adrenal steroidogenesis): ketoconazole, metyrapone, mitotane, etomidate
- Pituitary-directed (centrally-acting agents that suppress ACTH secretion by the pituitary; dopamine agonist: cabergoline and the somatostatin analog: pasireotide): cabergoline, pasireotide
- Glucocorticoid receptor-antagonizing drugs (blocks the peripheral effects of glucocorticoids): mifepristone Korlym (mifepristone) blocks the glucocorticoid receptor type II (GR-II) to which cortisol normally binds. By blocking this receptor, Korlym inhibits the effects of excess cortisol in CS patients. Because hypercortisolism often leads to hyperglycemia in patients with CS, the pivotal trial for Korlym was designed to measure changes in glucose levels in patients with glucose intolerance or type 2 diabetes mellitus. By blocking the glucocorticoid receptor, Korlym is able to help control hyperglycemia associated with CS.

Combination drug therapy for CS. No single medical or drug therapy has demonstrated complete efficacy in the treatment of CD or has proven effective in normalizing cortisol levels or managing all of the symptoms of CS. Adverse events are also not uncommonly encountered in patients on medical therapy. A strategy to increase treatment efficacy, whilst reducing doses of individual drugs and thereby minimizing adverse events, is to combine drugs with additive, synergistic, and/or complementary mechanisms of action.

PRACTICE GUIDELINES Treatment of Cushing’s syndrome: An Endocrine Society Clinical Practice Guideline (2015) Treatment of CS is essential to reduce mortality and associated comorbidities. Effective treatment includes the normalization of cortisol levels or action. It also includes the normalization of comorbidities via directly treating the cause of CS and by adjunctive treatments (e.g., antihypertensives). Surgical resection of the causal lesion(s) is generally the first-line approach. The choice of second-line treatments, including medication, bilateral adrenalectomy, and radiation therapy (for corticotrope tumors), must be individualized to each patient.

Cortisol levels remain unchanged or may increase during mifepristone treatment, and therefore practitioners cannot use hormonal measurements to guide efficacy or to diagnose adrenal insufficiency. Because practitioners must use clinical cortisol-dependent variables for these purposes, it is difficult to estimate the correct dose. For this reason, clinicians should start mifepristone at 300 mg/d, titrate it slowly, and base dose adjustment on clinical parameters, primarily glucose, and weight reduction. Adverse events include symptoms of cortisol insufficiency (fatigue, nausea, vomiting, arthralgias, and headache), evidence of increased mineralocorticoid action (hypertension, hypokalemia, edema), and

antiprogestin effects (endometrial thickening).
One study treated suspected adrenal insufficiency with drug discontinuation or 2–8 mg of dexamethasone daily (Fleseriu M, et al. 2012).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Korlym (mifepristone) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Korlym (mifepristone) include: pregnancy, concurrently taking CYP3A metabolized drugs (such as simvastatin, lovastatin) or CYP3A4 substrates with narrow therapeutic ranges (such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), receiving systemic corticosteroids for lifesaving purposes (e.g., immunosuppression after organ transplantation), women with a history of unexplained vaginal bleeding or with endometrial hyperplasia with atypia or endometrial carcinoma, known hypersensitivity to mifepristone or to any of the product components, do not use with hormonal contraceptives, avoid use with QT interval-prolonging drugs, or in patients with potassium channel variants resulting in a long QT interval.

OTHER SPECIAL CONSIDERATIONS:
Korlym (mifepristone) has a Black Boxed warning for termination of pregnancy. Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogestational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with KORLYM and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization, in which case no additional contraception is needed. Pregnancy must also be excluded if treatment is interrupted for more than 14 days in females of reproductive potential.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
miFEPRIStone TABS 300MG
Korlym TABS 300MG

REFERENCES

1. Korlym® tablets [prescribing information]. Menlo Park, CA: Corcept Pharmaceuticals; November 2019.
2. Belanoff JK, Rothschild AJ, Cassidy F, et al. An open-label trial of C-1073 (mifepristone) for psychotic major depression. Biol Psychiatry. 2002;52:386-392.
3. Fleseriu M, Biller BMK, Findling JW, et al. Mifepristone, a glucocorticoids receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrin Metab. 2012: 97(6):2039-2049.
4. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: A consensus statement. J Clin Endocrinol Metab. 2008;93:2454-2462.
5. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. Discov Med. 2012;13(69):171-179.
6. Rizk A, Honegger J, Milian M and Psaras T. Treatment options in Cushing's disease. Clin Med Insights

Oncol. 2012(6):75-84. 8. Mazziotti G, Gazzaruso C and Giustina A. Diabetes in Cushing syndrome: basic and clinical aspects. Trends Endocrinol Metab. 2011;22(12):499- 506.

7. Fleseriu, M., Auchus, R., Bancos, I., Ben-Shlomo, A., Bertherat, J., Biermasz, N. R., … Biller, B. M. (2021). Consensus on diagnosis and management of Cushing's Disease: A Guideline Update. The Lancet Diabetes & Endocrinology, 9(12), 847–875. doi:10.1016/s2213-8587(21)00235-7

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity Drug Class Contraindications/Exclusions/Discontinuation Available Dosage Forms	Q3 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy FDA-Approved Uses Contraindications/Exclusions/Discontinuation References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval FDA Approved Uses Contraindications/Exclusions/Discontinuation References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file