

PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Korlym® (mifepristone 300 mg tablets – Corcept)

DATE REVIEWED: 05/27/2020

OVERVIEW

Korlym 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.¹ Korlym should not be used for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome. Mifepristone, the active ingredient in Korlym is also available as Mifeprex® (mifepristone 200 mg tablets) indicated for the medical termination of intrauterine pregnancy through 70 days' pregnancy.² Mifeprex is not included in this *Prior Authorization* policy.

Mifepristone, the active ingredient in Korlym is a selective antagonist of the progesterone receptor (PR) at low doses and blocks the glucocorticoid type 2 receptor (GR-II) at higher doses.¹ Mifepristone has high affinity for the GR-II receptor but little affinity for the GR-I (mineralocorticoid) receptor (MR). In addition, mifepristone appears to have little or no affinity for estrogen, muscarinic, histaminic, or monoamine receptors. Mifepristone acts at the receptor level to block the effects of cortisol, and its antagonistic actions affect the hypothalamic-pituitary-adrenal (HPA) axis in such a way as to further increase circulating cortisol levels while at the same time blocking their effects. Mifepristone and its three active metabolites have greater affinity for the glucocorticoid receptor (100%, 61%, 48%, and 45%, respectively) than either dexamethasone (23%) or cortisol (9%).

Cushing's Disease

Endogenous Cushing's syndrome is a rare heterogeneous disorder with diverse causes that leads to cortisol excess (hypercortisolism).³ Patients with Cushing's syndrome exhibit a variety of signs and symptoms such as high blood pressure, diabetes, loss of libido, menstrual disorders, weight gain, hirsutism, acne, easy bruising, purplish skin striae, osteoporosis, muscle weakness, depression and cognitive impairment as a result of prolonged and inappropriately high exposure of tissue to glucocorticoids.³⁻⁴

The treatment of Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence and reversal of clinical features.⁵ Drug therapy plays an adjunctive role in patients with Cushing's syndrome and may help to improve the medical status of patients in preparation for surgery, and to control severe hypercortisolism in patients who are acutely ill, or in patients awaiting the effects of radiotherapy.⁶⁻⁹

Medications inhibiting adrenocortical steroidogenesis (ketoconazole tablets, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets] and etomidate injection) have been widely used in patients with Cushing's syndrome of varying causes.⁶ Ketoconazole tablets have a Food and Drug Administration (FDA) Orphan Drug Designation for the treatment of endogenous Cushing's syndrome.¹⁶ Ketoconazole and metyrapone (not commercially available in the US, may be obtained from the manufacturer on a compassionate use basis) are dose-dependent and reversible inhibitors of adrenal cortisol synthesis.^{6,8} Mitotane inhibits the synthesis of cortisol; however, at doses greater than 4 grams daily it causes cellular necrosis due to its irreversible effects on mitochondrial function, and therefore is primarily used in adrenal cancer.⁸ Signifor is a somatostatin analog indicated for the treatment of adults with Cushing's *disease* for whom pituitary surgery is not an option or has not been curative and works by decreasing

adrenocorticotrophic hormone (ACTH) secretion.¹³ The use of these drugs is limited by variable efficacy and adverse events (AEs).

The impairment of glucose metabolism generally resolves with normalization of cortisol levels because hypercortisolism is the causative factor for hyperglycemia.¹⁷

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Korlym. All approvals are provided for 1 year unless otherwise noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Korlym as well as the monitoring required for AEs, approval requires Korlym to be prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Korlym is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Endogenous Cushing's Syndrome.** Approve in patients who meet the following criteria (A, B, C, D and E):
 - A) Patient is ≥ 18 years of age; AND
 - B) Korlym is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome; AND
 - C) Korlym is being used to control hyperglycemia secondary to hypercortisolism in patients who have type 2 diabetes mellitus or glucose intolerance; AND
 - D) According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; AND

Note: For patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence*.

 - E) The patient meets one of the following (i or ii):
 - i. The patient has tried one of ketoconazole tablets, Metopirone (metyrapone capsules), Lysodren (mitotane tablets), or Signifor/Signifor LAR for the treatment of Cushing's syndrome; OR
 - ii. The patient is currently receiving Korlym.

Other Uses with Supportive Evidence

2. **Endogenous Cushing's Syndrome – Patients Awaiting Surgery.** Approve for 4 months if the patient meets the following criteria (A and B):
 - A) Patient is ≥ 18 years of age; AND
 - B) Korlym is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.
 3. **Endogenous Cushing's Syndrome – Patients Awaiting Response After Radiotherapy.** Approve for 4 months if the patient meets the following criteria (A and B):
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- A) Patient is \geq 18 years of age; AND
- B) Korlym is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Korlym has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Exogenous (Iatrogenic) Cushing's Syndrome.** Korlym is not indicated in exogenous Cushing's syndrome. Exogenous Cushing's syndrome is caused by excessive glucocorticoid administration.¹² Therefore, the process to reverse the excessive cortisol exposure is to taper or discontinue the offending drug when possible.
2. **Type 2 Diabetes Not Associated with Endogenous Cushing's Syndrome.** Korlym should not be used for the treatment of type 2 diabetes unrelated to endogenous Cushing's syndrome.¹
3. **Psychotic Features of Psychotic Depression.** Mifepristone has been used to treat the psychotic features of psychotic depression. Individual trials have demonstrated variable efficacy results.^{3,10-11,15,18} In some of the studies comparing mifepristone with placebo, various statistically significant improvements in psychiatric symptoms have been noted with mifepristone relative to placebo; however, the methodology and statistical analyses of some studies have been questioned.¹⁴ Data are inconclusive.
4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Korlym[®] tablets [prescribing information]. Menlo Park, CA: Corcept Pharmaceuticals; March 2020.
 2. Mifeprex[®] tablets [prescribing information]. New York, NY: Danco Laboratories, LLC; April 2019.
 3. 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.
 4. 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 Endocrinol Metab*. 2012; 97(6):2039-2049.
 5. 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.
 6. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. *Discov Med*. 2012;13(69):171-179.
 7. 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.
 9. 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.
 10. DeBattista C, Belanoff J, Glass S, et al. Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biol Psychiatry*. 2006;60:1343-1349.
 11. Flores BH, Kenna H, Keller J, et al. Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology*. 2006;31:628-636.
 12. Guaraldi F and Salvatori R. Cushing syndrome: maybe not so uncommon of an endocrine disease. *J Am Board Fam Med*. 2012;25:199-208.
 13. Signifor[®] injection [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2020.
 14. Carroll BJ and Rubin RT. Is mifepristone useful in psychotic depression? *Neuropsychopharmacology*. 2006;31:2793-2794.
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15. Blasey CM, Block TS, Belanoff JK and Roe RL. Efficacy and safety of mifepristone for the treatment of psychotic depression. *J Clin Psychopharmacol.* 2011;31:436-440.
 16. Food and Drug Administration. Search Orphan Drug Designations and Approvals Search term: Cushing's. Available at: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>. Accessed on April 3, 2020.
 17. Mazziotti G, Gazzaruso C and Giustina A. Diabetes in Cushing syndrome: basic and clinical aspects. *Trends Endocrinol Metab.* 2011;22(12):499-506.
 18. Block T, Petrides G, Kushner H, et al. Mifepristone plasma level and glucocorticoid receptor antagonism associated with response in patients with psychotic depression. *J Clin Psychopharmacol.* 2017;37(5):505-511.
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