

## PRIOR AUTHORIZATION POLICY

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

**TAC APPROVAL DATE:** 05/08/2019

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### 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>1</sup> 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).<sup>3</sup> 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.<sup>3-4</sup>

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.<sup>5</sup> 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.<sup>6-9</sup>

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.<sup>6</sup> Ketoconazole tablets have a Food and Drug Administration (FDA) Orphan Drug Designation for the treatment of endogenous Cushing's syndrome.<sup>16</sup> 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.<sup>6,8</sup> 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.<sup>8</sup> 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 adrenocorticotropic hormone (ACTH) secretion.<sup>13</sup> 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.<sup>17</sup>

### **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  $\geq 18$  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; 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 prescribing physician, the patient is not a candidate for surgery or surgery has not been curative; AND
  - E) 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.

#### **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  $\geq 18$  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.
- 3. Endogenous Cushing's Syndrome, Patients Awaiting Response After Radiotherapy.** Approve for 4 months if the patient meets the following criteria (A and B):
  - 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 are 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.<sup>12</sup> 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.<sup>1</sup>
- 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.<sup>3,10-11,15,18</sup> 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.<sup>14</sup> 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; May 2017.
2. Mifeprex® tablets [prescribing information]. New York, NY: Danco Laboratories, LLC; April 2019.
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16. Food and Drug Administration. Search Orphan Drug Designations and Approvals Search term: Cushing’s. Available at: <http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm>. Accessed on April 30, 2019.
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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.

**OTHER REFERENCES UTILIZED**

- Morgan FH, Laufgraben MJ. Mifepristone for Management of Cushing’s Syndrome. *Pharmacotherapy.* 2013;33(3):319-329.

**HISTORY**

Type of Revision	Summary of Changes*	TAC Approval Date
Annual Revision	No criteria changes	04/13/2016
Annual Revision	No criteria changes	04/12/2017
Annual Revision	Updated policy title to include Cushing’s. The requirement that Korlym be prescribed by an endocrinologist was modified to add “a physician who specializes in the treatment of Cushing’s syndrome”. A requirement was added to align with the FDA-approved indication to add that Korlym is being used to control hyperglycemia secondary to hypercortisolism in patients who have type 2 diabetes mellitus or glucose intolerance.	05/23/2018
Selected revision	Added Signifor LAR as option of previous therapies.	09/12/2018
Annual revision	Endogenous Cushing’s Syndrome: the length of approval was updated from 3 years to 1 year. Cushing’s Syndrome – Patients Awaiting Surgery: the length of approval was updated from 2 months to 4 months to align with other Cushing’s policies. Created separate approval condition for Cushing’s Syndrome – Patients Awaiting Therapeutic Response for Radiotherapy with a 4 month approval duration.	05/08/2019

\*For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>. TAC – Therapeutic Assessment Committee; NA – Not applicable.