Korlym (mifepristone)

Policy

BCBSKC will provide coverage for Korlym when it is determined to be medically necessary because the following criteria are met.

When Policy Topic is covered:
The use of Korlym may be considered medically necessary for the following:

Endogenous Cushing’s syndrome. Approve in patients who meet the following criteria (a, b, c, and d):
   a) Patient is ≥ 18 years of age; AND
   b) Korlym is prescribed by or in consultation with an endocrinologist; AND
   c) According to the prescribing physician, the patient is not a candidate for surgery or surgery has not been curative; AND
   d) The patient has tried ketoconazole tablets, Metopirone (metrapone capsules), or Lysodren (mitotane tablets), or Signifor for the treatment of Cushing’s syndrome.

Korlym is 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. Patients enrolled in the pivotal trial for Korlym had or were not candidates for surgery or radiotherapy.

Although Korlym is specifically indicated to control hyperglycemia secondary to endogenous Cushing’s syndrome in adults with type 2 diabetes or glucose intolerance, improvement in the manifestations of Cushing’s syndrome were demonstrated in both patients with diabetes or glucose intolerance at baseline and in patients without diabetes or glucose intolerance at baseline. The overall response rate in patients treated with Korlym (secondary endpoint) was 87% (95% CI lower bound: 76%; P < 0.0001); response rates were similar in the diabetes and hypertension cohorts (mITT = 46). Response rate assessment included glucose homeostasis, blood pressure, lipids, weight and body composition change, clinical appearance (acne, hirsutism, striae, and Cushingoid appearance), strength, neuropsychological parameters (BDI-II and Trail Making Test), and quality of life parameters (SF-36 Health Survey version 2). Additional data used to determine clinical improvement included changes in diabetes and hypertension medication, HbA1c, insulin sensitivity, metabolic function, weight, and body composition.

In general, the initial treatment of choice for Cushing’s disease (that is Cushing’s syndrome caused by a pituitary adenoma) is selective pituitary adenectomy by a surgeon with extensive demonstrated experience in pituitary surgery. Among patients with ectopic ACTH secretion surgical resection of the underlying tumor is advised; however, the underlying tumor may be metastatic or otherwise unresectable. In patients with adrenal adenoma causing Cushing’s syndrome unilateral adrenalectomy will generally result in clinical cure, whereas patients with adrenocortical carcinoma usually have an unfavorable prognosis. In the event of failure after initial or repeat pituitary surgery, second-line treatment options include medical therapy, radiotherapy or bilateral adrenalectomy, where applicable.
Drug therapy plays an adjunctive role in patients with Cushing's syndrome.\textsuperscript{6-8} Medications inhibiting adrenocortical steroidogenesis (ketoconazole, Metopirone, Lysodren, and etomidate injection) have been widely used in patients with Cushing's syndrome of varying causes.\textsuperscript{6} Ketoconazole tablets have a FDA Orphan Drug Designation for the treatment of endogenous Cushing's syndrome.\textsuperscript{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.\textsuperscript{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.\textsuperscript{8}

In patients with endogenous Cushing's syndrome control of hypercortisolism is the first step to managing hyperglycemia taking into account various treatments may affect the outcome of diabetes regardless of cortisol excess.\textsuperscript{8} The impairment of glucose metabolism generally resolves with normalization of cortisol levels.

**Other Uses with Supportive Evidence**

2. **Patients with Endogenous Cushing’s syndrome awaiting surgery.** Approve for 2 months if the patient meets the following criteria (a and b):
   a) Patient is ≥ 18 years of age; AND
   b) Korylm is prescribed by or in consultation with an endocrinologist.

   In the opinion of a specialist reviewing the data we have adopted this criterion.

   The role of drug therapy in patients with Cushing's syndrome is generally adjunctive 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.\textsuperscript{6-8}

**When Policy Topic is not covered:**
The use of Korylm is considered investigational for all other indications including:

1. **Exogenous (iatrogenic) Cushing’s syndrome.** Korylm is not indicated in exogenous Cushing’s syndrome. Exogenous Cushing's syndrome is caused by excessive glucocorticoid administration.\textsuperscript{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.** Korylm should not be used for the treatment of type 2 diabetes unrelated to endogenous Cushing’s syndrome.\textsuperscript{1}

3. **Psychotic features of psychotic depression.** The manufacturer is conducting Phase III studies with mifepristone to treat the psychotic features of psychotic depression.\textsuperscript{9} Mifepristone is being investigated as an alternative to electroconvulsive therapy (ECT) or combination drug therapy to determine whether patients with psychotic features of psychotic depression who are treated with mifepristone can be more easily maintained on antidepressant therapy alone without the need for ECT or antipsychotic medication. Individual trials have demonstrated variable efficacy results.\textsuperscript{3,10-11,15} A Phase III study is ongoing to further evaluate the efficacy and safety of mifepristone in the treatment of psychotic depression.\textsuperscript{13} 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.\textsuperscript{14} Data are inconclusive.

**Considerations**
Korylm requires prior authorization through the Clinical Pharmacy Department.
This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Hayes Medical Technology Directory, Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

**Description of Procedure or Service**

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 is also available as Mifeprex\(^{\circ}\) [mifepristone 200 mg tablets] indicated for the medical termination of intrauterine pregnancy through 49 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%).

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.\(^5\)\(^-\)\(^8\)

Medications inhibiting adrenocortical steroidogenesis (ketoconazole tablets, Metopirone\(^{\circ}\) [metyrapone capsules], Lysodren\(^{\circ}\) [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.\(^6\) 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 ACTH secretion.\(^17\) The use of these drugs is limited by variable efficacy and adverse events (AEs).

**Rationale**

The efficacy and safety of Korlym were established in one uncontrolled, open-label, 24-week, multicenter (US), pivotal trial (the Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing’s Syndrome [SEISMIC]) in 50 adults with Cushing’s syndrome and type 2 diabetes mellitus, impaired glucose tolerance, or a diagnosis of hypertension (systolic blood pressure...
[SBP] > 140 mm Hg and diastolic blood pressure [DBP] > 90 mm Hg) who had failed multi-modal standard therapy (surgical treatment and/or radiotherapy). Among enrolled patients, 43 patients (86%) had Cushing’s disease (pituitary adenoma), [42 patients failed previous surgery; 18 patients also had pituitary radiation (time from radiation was 32 ± 7 months); 1 patient had not previously had surgery], 4 patients (8%) had ectopic adrenocorticotropic hormone (ACTH) secretion, and 3 patients (6%) had adrenal carcinoma. Patients with diabetes and hypertension were enrolled into the diabetes cohort.

Results. In the diabetes cohort, 15 of 25 patients (60%) were treatment responders (95% confidence interval [CI] lower bound: 42%; P < 0.0001) as assessed by ≥ 25% reduction in area-under-the-concentration-time-curve for glucose (AUC$_{glucose}$) from baseline. The median decrease in AUC$_{glucose}$ was 35%. In the hypertension cohort, DBP response (≥ 5 mmHg reduction from baseline) was reported in 8 of 21 patients (38%) [95% CI lower bound: 21%; P < 0.05]. The overall response rate (secondary endpoint) as assessed by a data review board in the modified intent-to-treat (mITT) population (n = 46) was 87% (95% CI lower bound: 76%; P < 0.0001); response rates were similar in the diabetes and hypertension cohorts. Response rate assessment included glucose homeostasis, blood pressure, lipids, weight and body composition change, clinical appearance (acne, hirsutism, striae, and Cushingoid appearance), strength, neuropsychological parameters (Beck Depression Inventory [BDI-II] and Trail Making Test), and quality of life parameters (Short Form 36 [SF-36] Health Survey version 2). Additional data used to determine clinical improvement included changes in diabetes and hypertension medication, glycosylated hemoglobin (HbA$_{1C}$), insulin sensitivity, metabolic function, weight, and body composition.

Mean baseline HbA$_{1C}$ was 7.43 ± 1.52% in the diabetes cohort and decreased to 6.29 ± 0.99% at Week 24/early termination (ET) [P < 0.001]. Fasting plasma glucose (FPG) was reduced from 149 ± 74.7 mg/dL to 104 ± 37.5 mg/dL (P < 0.03). Antidiabetic medications were reduced in 7 of the 15 diabetes patients taking antidiabetic medications at baseline. Among patients taking insulin (n = 12) five patients reduced their daily insulin dose by ≥ 50%. In the mITT population (n = 46), mean change in weight from baseline was -5.7 ± 1.5% (P < 0.001); 52% of patients lost ≥ 5% of their baseline weight. Waist circumference decreased by 6.8 ± 5.8 cm from baseline (P < 0.001). Mean percentage of body fat was reduced by 3.6% at Week 24 (P < 0.001). Absolute fat mass decreased by 13.9% for the total body (P < 0.001), 15.6% for the trunk (P < 0.001), and 17.1% for the abdominal region (P < 0.001). Among patients with hypertension at baseline (n = 40), 42.5% of patients had ≥ 5 mmHg reduction in DBP from baseline at Week 24/ET and 27.5% of patients had reductions in antihypertensive medications. Overall, 52.5% (95% CI: 36.13, 68.49) of patients with hypertension had a DBP response or reduction in antihypertensive medications; however, there were no significant differences in the mean SBP and DBP from baseline to Week 24/ET among this population of patients. Median BDI-II depression scores improved in the mITT population (baseline score: 14.5, range 0 to 49; Week 24/ET score: 9.5, range 0 to 36; P < 0.001). Cognition scores measured by the TRAIL Making Test at Week 24/ET were improved (median decrease of 4 seconds in Trail A and median decrease of 12 seconds in Trail B; P < 0.01 for each, respectively). Quality of life was improved from baseline at Week 24/ET as measured by SF-36 mental composite scores (mean score 40 ± 14.5 vs. 45.4 ± 12.5; P = 0.01) and physical composite scores (mean 34.9 ± 11.0 vs. 39.1 ± 10.8; P = 0.02).

References:


Other References Utilized


**Billing Coding/Physician Documentation Information**

N/A Korlym is considered a pharmacy benefit.

**Additional Policy Key Words**

Policy Number: 5.01.545

**Related Topics**

N/A

**Policy Implementation/Update Information**

06/2013 New Policy titled Korlym
05/2014 Policy reviewed – no changes made

This Medical Policy is designed for informational purposes only and is not an authorization, an explanation of benefits, or a contract. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member’s benefit plan to determine if there is any exclusion or other benefit limitations.
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