Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome

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This peer-reviewed publication reports pre-specified endpoints that are not provided in detail and/or are inconsistent with the FDA-approved Prescribing Information for Korlym® (mifepristone) 300 mg Tablets, a product of Corcept Therapeutics.
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Context: Cushing’s syndrome (CS) is a disorder associated with significant morbidity and mortality due to prolonged exposure to high cortisol concentrations.

Objective: Our objective was to evaluate the safety and efficacy of mifepristone, a glucocorticoid receptor antagonist, in endogenous CS.

Design and Setting: We conducted a 24-wk multicenter, open-label trial after failed multimodality therapy at 14 U.S. academic medical centers and three private research centers.

Participants: Participants included 50 adults with endogenous CS associated with type 2 diabetes mellitus/impaired glucose tolerance (C-DM) or a diagnosis of hypertension alone (C-HT).

Intervention: Mifepristone was administered at doses of 300-1200 mg daily.

Main Outcome Measures: We evaluated change in area under the curve for glucose on 2-h oral glucose test for C-DM and change in diastolic blood pressure from baseline to wk 24 for C-HT.

Results: In the C-DM cohort, an area under the curve for glucose (AUCglucose) response was seen in 60% of patients (P < 0.0001). Mean ± SD glycated hemoglobin (HbA1c) decreased from 7.43 ± 1.52% to 6.29 ± 0.99% (P < 0.001); fasting plasma glucose decreased from 149.0 ± 75.7 mg/dl (8.3 ± 4.1 mmol/liter) to 104.7 ± 37.5 mg/dl (5.8 ± 2.1 mmol/liter, P < 0.03). In C-HT cohort, a diastolic blood pressure response was seen in 38% of patients (P < 0.05). Mean weight change was −5.7 ± 7.4% (P < 0.001) with waist circumference decrease of −6.78 ± 5.8 cm (P < 0.001) in women and −8.44 ± 5.9 cm (P < 0.001) in men. Overall, 87% (P < 0.0001) had significant improvement in clinical status. Insulin resistance, depression, cognition, and quality of life also improved. Common adverse events were fatigue, nausea, headache, low potassium, arthralgia, vomiting, edema, and endometrial thickening in women.

Conclusions: Mifepristone produced significant clinical and metabolic improvement in patients with CS with an acceptable risk-benefit profile during 6 months of treatment. (J Clin Endocrinol Metab 97: 2039–2049, 2012)
Cushing’s syndrome (CS), is a serious endocrine disorder that may be caused by a pituitary [Cushing’s disease (CD)] or nonpituitary (ectopic) ACTH-secreting tumor or by an adrenal neoplasm. If inadequately treated, CS is associated with a 3.8- to 5.0-fold higher mortality than the general population (1–3). Regardless of cause, surgery is usually the treatment of choice; however, complete removal of the neoplasm may not be possible (4, 5). Adjunctive radiotherapy for CD may take years to control excess cortisol (6). Laparoscopic bilateral adrenalectomy represents another treatment option. No medical treatments were approved by the U.S. Food and Drug Administration for CS when the study was conducted, but off-label use of several medications is common, including dopamine agonists, somatostatin analogs, and the adrenal steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, and etomidate) (4, 7). Ketoconazole and mitotane are effective in many patients, but in CD, doses may need progressive increases due to escape from cortisol blockade. The tolerability of these drugs, especially at higher doses, limits their use in some patients (8, 9).

Mifepristone ([11β-[P-(dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one] is a progesterone receptor antagonist that has glucocorticoid receptor antagonist activity at higher concentrations, with more than three times the binding affinity for the glucocorticoid receptor than dexamethasone (10, 11). It does not bind to the mineralocorticoid receptor (9). Case reports and small retrospective studies of mifepristone treatment in CS document improvements in abnormal glucose metabolism, psychiatric symptoms, and the somatic changes associated with CS; hypokalemia was the most commonly reported side effect (9, 12–25). Based on these preliminary findings, an open-label, prospective, multicenter, 6-month study of the safety and efficacy of mifepristone was conducted in patients with endogenous CS refractory to other therapies.

**Patients and Methods**

**Patients**

Adults with confirmed endogenous CS who had associated type 2 diabetes mellitus (T2DM), impaired glucose tolerance (IGT), or a diagnosis of hypertension (HTN) were enrolled (Fig. 1). Endogenous hypercortisolism was defined as elevated urinary free cortisol on at least two 24-h collections and elevated late-night salivary cortisol and/or lack of suppression with dexamethasone. T2DM was defined as a fasting plasma glucose (FPG) of at least 126 mg/dl (≥7.0 mmol/liter) on two measurements or a 2-h plasma glucose of at least 200 mg/dl (≥11.1 mmol/liter) after a 75-g oral glucose tolerance test (oGTT), and IGT was defined as 2-h oGTT glucose value of 140–199 mg/dl (7.8–11.0 mmol/liter). HTN was defined as systolic blood pressure over 140 mm Hg and/or diastolic blood pressure (DBP) over 90 mm Hg or pharmacologically treated HTN.

At least two of the following signs or symptoms of Cushing’s were also necessary for inclusion: Cushimgoid appearance (moon facies, dorsocervical fat pad, and plethora), increased body weight or central obesity, proximal muscle weakness, low bone mineral density (T score < –1.0), psychiatric symptoms, and skin changes (hirsutism, violaceous striae, or acne).

Patients were excluded for poorly controlled diabetes mellitus [glycated hemoglobin (HbA1c) ≥11%], poorly controlled HTN (>170/110 mm Hg), use of drugs to treat hypercortisolism within 1 month of baseline (mitotane for adrenal carcinoma was allowed if on stable dose ≥1 month before entry), uncorrected hypokalemia, or uncontrolled hypothyroidism or hyperthyroidism; also excluded were women with a uterus who required anticoagulants or had hemorrhagic disorders, endometrial hyperplasia, carcinoma, or polyps. Increases or additions of antihyperglycemic medications during the study were not permitted for patients with T2DM/IGT. For patients with HTN, increases or additions of antihypertensive medications were not permitted with the exception of mineralocorticoid receptor antagonists, which were allowed for treating hypokalemia, a known side effect of mifepristone (9). Changes in or initiation of antidepressant or lipid-lowering medications were not allowed.

The study was approved by the institutional review board at each center and was registered with www.clinicaltrials.gov (NCT00569582). All patients provided written informed consent.

**Design**

This was a 24-wk, open-label, multicenter study of mifepristone administered as a single daily oral dose. Treatment began at 300 mg/d; if no significant clinical improvement was noted by the investigator, doses could be increased to 600 mg/d on d 14, 900 mg/d at wk 6, and 1200 mg/d at wk 10. Dose interruption and reduction were specified in the protocol for the following adverse events (AEs): adrenal insufficiency (AI), severe hypokalemia,
and vaginal bleeding. Temporary glucocorticoid rescue for suspected AI was also allowed.

Assessments

The primary endpoint for patients with CS and T2DM/IGT (C-DM cohort) was the change in area under the curve for glucose ($\text{AUC}_{\text{glucose}}$) on oGTT from baseline to wk 24. Response was defined as at least a 25% decrease in $\text{AUC}_{\text{glucose}}$ an amount considered clinically meaningful improvement in glucose control (26). $\text{AUC}_{\text{glucose}}$ was used because both patients with T2DM and patients with IGT were enrolled, and HbA1c and FPG would not be uniformly applicable. In patients receiving medications for diabetes, administration occurred before the oGTT (other than short-acting insulin and glucagon-like peptide-1 analogs). The primary endpoint for patients with CS and a diagnosis of HTN (C-HT cohort) was the change in DBP from baseline to wk 24; response was defined as DBP decrease of at least 5 mm Hg (mean of two sequential readings). Patients with both T2DM/IGT and HTN were included only in the C-DM cohort.

Key secondary endpoints included clinical response graded by an independent data review board (DRB) at wk 6, 10, 16, and 24 compared with baseline. The DRB consisted of three CS experts who evaluated the following assessments: glucose homeostasis, blood pressure, lipids, weight and body composition change, clinical appearance (acne, hirsutism, striae, and Cushingoid appearance) (27, 28) as rated by the investigators, strength, and neuropsychological [Beck Depression Inventory (BDI)-II and Trail Making Test] (29–31) and quality of life [Short-Form 36 Health Survey version 2 (SF-36)] (32) parameters. The DRB also reviewed standardized photographs of 34 consenting patients. Visit number after baseline and mifepristone dose were blinded. Each DRB member categorized patient overall status at follow-up visits as worse (−1), unchanged (0), or having clinically significant improvement (+1) from baseline. If the reviewers’ median score was +1, the patient was considered to have clinical improvement.

Blood, urine, and saliva samples were analyzed by a central laboratory (Quest Diagnostics, Collegeville, PA). $\text{AUC}_{\text{glucose}}$ and $\text{AUC}_{\text{insulin}}$ were determined using the linear trapezoidal rule; homeostatic model assessment of insulin resistance (HOMA-IR) was calculated (33). Urinary and salivary cortisol levels were assayed with liquid chromatography tandem mass spectrometry [normal ranges, respectively, are 2–42.4 $\mu$g/24 h (5.5–117 nmol/24 h) and ≤0.09 $\mu$g/dl (2.5 nmol/liter)]; serum cortisol [normal range is 4–22 $\mu$g/dl (110–607 nmol/24 h)], and ACTH (normal range is 5–27 pg/ml (1.1–5.9 pmol/liter) for females and 7–50 pg/ml (1.5–11 pmol/liter) for males) were measured with immunoenzymimetric assay.

AEs were reviewed every visit, and patients were monitored with vital signs, physical exams, and blood tests; transvaginal ultrasounds were conducted at baseline, wk 24 [or early termination (ET)], and 6 wks after last dose. Pituitary magnetic resonance imaging (MRI) was performed at screening and at wk 10 and 24 (or ET) in patients with CD. Body composition was measured using dual-energy x-ray absorptiometry at baseline and wk 24 or ET using Hologic (Bedford, MA) or GE Lunar (Madison, WI) instruments; results were submitted to a central reading site for quality control and analysis.

Statistics

Patients who took at least one dose of study medication comprised the safety population (n = 50). A modified intent-to-treat (mITT) population (patients who received ≥30 d of study medication) was used for analyses of efficacy (n = 46). The completer population included participants who completed through wk 24 and were at least 80% compliant with study medication (n = 33).

Because there was no placebo group in this study, a responder analysis was conducted. Responder rates were tested against an a priori threshold of 20%, which was chosen based on very low spontaneous response rates in this patient population (<5%) (34). The null hypothesis was to be rejected if the lower bound of the one-sided binomial 95% confidence interval (CI) of responder rates was over 20%. Because mifepristone blocks rather than lowers cortisol, alternative quantitative endpoints (other than cortisol) were assigned at study entry based on inclusion in either C-DM or C-HT cohorts. Two abnormal oGTTs were required for inclusion in the C-DM group; patients with a diagnosis of HTN and without T2DM/IGT were included in the C-HT group. For statistical analysis, response was defined as at least 25% reduction in $\text{AUC}_{\text{glucose}}$ for C-DM patients or at least 5 mm Hg reduction in DBP in C-HT patients comparing baseline with wk 24/ET. For patients who did not complete the study or have an ET visit, the last available data were used. ANOVA and $t$ tests were used for analyses of other endpoints. Nonparametric statistical testing was employed for nonnormally distributed data. Change in oGTT curves over the course of the study was modeled by a hierarchical linear mixed model that took into consideration the correlation within subjects. SAS statistical software versions 9.1.3 and 9.2 (Cary, NC) were used. Data are shown as mean ± SD unless otherwise stated.

Results

Patients

From January 2008 to January 2011, 50 patients with CS were enrolled at 17 U.S. centers; 34 completed the study. Forty-three patients had a pituitary source of CS (42 with unsuccessful pituitary surgery, 18 with pituitary radiation, and one without previous surgery), four had ectopic ACTH secretion, and three had adrenal cortical carcinoma. Baseline characteristics are detailed in Tables 1 and 2. The mean dose ± SD at the final study visit was 732 ± 366 mg/d. Twenty-two subjects received the maximum dose of 1200 mg/d. Dose interruptions occurred in 42% of patients with median duration of 2 d (range 1–39 d). There were 18 dose reductions in 12 patients; reductions occurred most commonly in 300-mg decrements (317 ± 114 mg).

Primary efficacy analyses

Patients with T2DM/IGT

In the C-DM mITT population, $\text{AUC}_{\text{glucose}}$ decreased by at least 25% on oGTT in 15 of 25 (60%) patients from baseline to wk 24/ET (95% CI lower bound 42%, P < 0.0001) with a median decrease of 36% [303±30.0 mg/dl·120 min (1683.3 mmol/liter·120 min) to 2065.5 mg/dl·120 min (1146.4 mmol/liter·120 min)] as well as comparable reductions in plasma glucose levels (Fig. 2 and
Similar reductions in AUC_{glucose} were observed in the C-DM ITT and completer populations. The most common doses among responders at wk 24/ET were 600 mg (40%) and 1200 mg (40%), followed by 300 mg (13.3%) and 900 mg (6.7%). In exploratory analyses we found no relationship between the incremental change in dose from baseline and AUC_{glucose} (see Supplemental Fig. 1, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org).

### Patients with HTN

In the C-HT mITT cohort, eight of 21) patients (38.1%) achieved the primary endpoint of at least 5 mm Hg decline in DBP (95% CI lower bound 21%, \( P < 0.05 \); Table 3). Four patients (two responders) received spironolactone during the study; one nonresponder was on spironolactone at entry and remained on a stable dose throughout the study.

### Secondary endpoints

#### Clinical improvement

The overall clinical improvement response rate as assessed by the DRB in the mITT population was 87% (95% CI lower bound 76%, \( P < 0.0001 \)); response rates were similar in the C-DM and C-HT cohorts (Table 3). Thirty-three patients
(72%) had a median score of +1 at wk 24 or ET. Eleven patients by wk 6 and another six patients by wk 10 had a median score of +1 with responses maintained throughout the remainder of the study (Initial clinical improvement response by dose and visit are shown in Supplemental Fig. 2). Three patients had a nonsustained improvement (median score of +1 decreased to 0 at wk 24 or ET). One patient was rated as being worse at the final visit (early termination at wk 10) than at baseline.

Other glucose-related endpoints
FPG decreased from 149.0 ± 74.7 mg/dl (8.3 ± 4.1 mmol/liter) at baseline to 104.7 ± 37.5 mg/dl (5.8 ± 2.1 mmol/liter) at wk 24 (P < 0.03). Antidiabetic medications were reduced in seven of 15 patients. Of 12 patients taking insulin, five reduced their daily dose by at least half. Eighteen of 25 C-DM patients (72%) had at least a 25% reduction from baseline in AUCglucose or a reduction in antidiabetic medication (95% CI = 50.6–

### TABLE 3. Summary of responder analyses (mITT population)

<table>
<thead>
<tr>
<th>Statistics (mITT population)</th>
<th>Responder [n (%)]</th>
<th>Nonresponder [n (%)]</th>
<th>Lower bound one-sided 95% exact binomial CI (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-DM (n = 25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with or without a 25% reduction from baseline in AUCglucose at wk 24/ET</td>
<td>15 (60)</td>
<td>10 (40)</td>
<td>41.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C-HT (n = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET</td>
<td>8 (38.1)</td>
<td>13 (61.9)</td>
<td>20.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C-HT and C-DM with HTN at screening (n = 40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET</td>
<td>17 (42.5)</td>
<td>23 (57.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants who had a reduction in antihypertensive medications at wk 24/ET</td>
<td>11 (27.5)</td>
<td>29 (72.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants who had either ≥5 mm Hg reduction from baseline in DBP or had a reduction in antihypertensive medications at wk 24/ET</td>
<td>21 (52.5)a</td>
<td>19 (47.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median clinical improvement score of +1 at any reviewed visitb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined cohorts (n = 46)</td>
<td>40 (87.0)</td>
<td>6 (13.0)</td>
<td>75.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C-DM (n = 25)</td>
<td>23 (92.0)</td>
<td>2 (8.0)</td>
<td>76.9</td>
<td></td>
</tr>
<tr>
<td>C-HT (n = 21)</td>
<td>17 (81.0)</td>
<td>4 (19.0)</td>
<td>61.6</td>
<td></td>
</tr>
</tbody>
</table>

a 95% CI = 36.1–68.5.

b For overall clinical improvement (median DRB score +1) at any reviewed visit, the null hypothesis was to be rejected in favor of the alternative if the lower limit of the 95% exact one-sided binomial CI for the responder rate was at least 30%.
87.9%). The mean baseline HbA1c of 7.43 ± 1.52% in the C-DM group decreased to 6.29 ± 0.99% at wk 24/ET (P < 0.001) (Fig. 3A). Twelve C-DM patients had an HbA1c over 7% at baseline (mean 8.53 ± 1.11%); of these, nine achieved an HbA1c below 7%, including six reaching an HbA1c of 6% or below. C-DM and C-HT patients were insulin resistant and demonstrated rapid and significant improvements in AUC_insulin, which continued throughout the study (Fig. 3B); HOMA-IR demonstrated improvements in insulin sensitivity (Fig. 3C).

**Weight and body composition**

In the mITT population (n = 46), mean ± SD body weight change from baseline (99.5 kg) to wk 24/ET was −5.7 ± 7.4% (P < 0.001) (Fig. 4A). Twenty-four patients lost at least 5% of their baseline weight, 12 of whom lost at least 10%; 10 patients gained an average of 3.6 ± 3.9%. Waist circumference decreased by −6.8 ± 5.8 cm (P < 0.001) in women and −8.4 ± 5.9 cm in men (P < 0.001) (Fig. 4B). Mean percent total body fat declined by 3.6% by wk 24 (P < 0.001). Absolute fat mass declined by 13.9% (P < 0.001) for the total body, 15.6% (P < 0.001) for the trunk, and 17.1% (P < 0.001) for the abdominal region (Fig. 4C).

**DBP and antihypertensive medications (C-HT and C-DM with HTN)**

In addition to the 21 C-HT patients, 19 C-DM patients had a diagnosis of HTN at study entry; 42.5% (17 of 40) of these had a reduction in DBP of at least 5 mm Hg at wk 24/ET compared with baseline, and 27.5% had reductions in antihypertensive medications (50% of patients with a diagnosis of HTN were taking at least two antihypertens-
sive medications at baseline). Overall, 52.5% (95% CI = 36.13–68.49%) had either a response in DBP or a reduction in antihypertensive medications (Table 3). However, there were no significant differences in mean systolic blood pressure and DBP from baseline to wk 24/ET among C-HT patients (129.5 ± 16.3/82.9 ± 11.4 vs. 129.9 ± 19.0/82.8 ± 13.2 mm Hg) or in C-DM patients with a diagnosis of HTN (137.7 ± 24.0/86.4 ± 15.3 vs. 132.2 ± 16.7/82.4 ± 13.2 mm Hg). Eight of 12 patients with DBP of at least 90 mm Hg at study entry had a reduction of at least 5 mm Hg (median decline −14 mm Hg, range −26.5 to −5.5 mm Hg); only one (C-DM patient) of the eight received additional antihypertensive therapy. AEs of increased blood pressure were reported in 12 patients, nine (75%) of whom had evidence of mineralocorticoid recep-

tor activation (edema, hypokalemia, and/or need for spironolactone to control hypokalemia).

**Mood, cognition, and quality of life**

Median BDI-II depression scores improved in the mITT population (baseline 14.5, range 0–49; wk 24/ET 9.5, range 0–36; P < 0.001). For patients with at least mild depression at baseline (BDI-II ≥ 14, n = 24), median BDI-II scores improved from 23 (range 14–49) to 12 (range 0–34) (P < 0.001). Cognition scores were measured by the Trail Making Test at wk 24/ET; there were improvements in both Trail A (median decrease of 4.0 sec, P < 0.01) and Trail B (median decrease of 12 sec, P < 0.01). Quality of life improved at wk 24/ET as measured by SF-36 mental composite scores (mean 40.0 ± 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).

**Hormone and pituitary MRI scan changes**

During mifepristone treatment, 72% of the 43 patients with CD had at least a 2-fold increase in ACTH, cortisol, or both; 28% had smaller increases. These changes were observed early (by d 14), plateaued from wk 10–24, and declined to baseline levels at the follow-up visit 6 wk after discontinuation of mifepristone. Increases in ACTH of at least 2-fold were observed in 62.8% of patients; 33.6% had lesser increases, and 4.7% had no change. Late-night salivary cortisol increased 7.92-fold (1.43) at wk 16, and urinary free cortisol increased 7.70-fold (15.29) at wk 24/ET. At the 6-wk follow-up visit, ACTH and cortisol (serum and urine) declined to near baseline levels. Patients with ectopic ACTH secretion did not demonstrate increases in ACTH and cortisol in response to mifepristone.

Pituitary MRIs were obtained in 41 CD patients; 17 had visible tumors, 10 of which were macroadenomas, and the remaining 24 did not have demonstrable tumors after surgery. MRIs were stable at wk 10 and 24 in all cases except one. This patient had an aggressive pituitary tumor at baseline that was increased in size at wk 10, leading to treatment discontinuation.

**Safety**

Overall, AEs were reported in 88% of patients during mifepristone treatment, most commonly nausea (48%), fatigue (48%), headache (44%), decreased blood potassium (34%), arthralgia (30%), vomiting (26%), peripheral edema (26%), HTN (24%), dizziness (22%), decreased appetite (20%), and endometrial thickening (20%). The majority of AEs were considered mild or moderate. Seven patients discontinued mifepristone because of an AE; fatigue was the only cause of discontinuation for more than one patient (n = 2). Interruptions or reductions in mifepristone due to AEs, most commonly nausea (n = 6), occurred in 40% of patients; there were interruptions or reductions for protocol-specified events in four subjects (two for AI, one for severe hypokalemia, and one for vaginal bleeding). After dose interruption or reduction before wk 10, there were increases in dose in one of four and two of five patients, respectively; after wk 10, dose escalation did not occur after an interruption for an AE except in a single patient. Four patients experienced progression of preexisting metastatic malignancy that resulted in death.

AI was reported in two patients. One occurred during an infection and responded to withdrawal of mifepristone; the other resolved with mifepristone withdrawal and dexamethasone administration (6–9 mg by mouth daily for 6 d). Neither episode was associated with hypoglycemia or hypotension, and mifepristone was restarted at a lower dose. Analysis of AEs and concomitant medications identified five other instances of two or more symptoms possibly consistent with AI during which glucocorticoids were administered. Dexamethasone doses for these episodes ranged from 2–8 mg daily in tapering amounts for 1–12 d. Vaginal bleeding was observed during the study in five premenopausal women. Prolonged metrorrhagia was observed in two of them after discontinuing mifepristone. Endometrial thickening was reported as an AE in 10 women. Three women underwent dilatation and curettage for unresolved endometrial thickening.

Twenty-two patients had a serum potassium level less than 3.5 mEq/liter (<3.5 mmol/liter), but only three experienced severe hypokalemia [<2.5 mEq/liter (<2.5 mmol/liter)] during mifepristone treatment, including one serious AE [potassium 2.1 mEq/liter (2.1 mmol/liter)]. Hypokalemia occurred in patients with both ACTH-dependent and independent CS. Four (one adrenal cancer and three ectopic ACTH) of seven patients with nonpituitary CS experienced hypokalemia during treatment. Hypokalemia was often associated with alkalosis and edema and generally responded to potassium replacement (10–420 mEq daily); all nonpituitary CS patients received potassium supplementation. Overall, spironolactone (50–400 mg daily) was used by 14 patients; it was started or increased in 11 patients for hypokalemia while taking mifepristone, including one patient with adrenal cancer and two patients with ectopic ACTH secretion. Reversible decreases in high-density lipoprotein cholesterol (HDL-C) and increases in TSH were observed. The mean change in HDL-C from baseline [62.3 ± 27.8 mg/dl (1.61 ± 0.72 mmol/liter)] to wk 24/ET was −14.2 ± 11.9 mg/dl (0.37 ± 0.31 mmol/liter) (P < 0.001); there were small declines in low-density lipoprotein cholesterol and triglycerides that were not statistically significant. Eight patients had undetectable TSH at baseline; of the remaining 42 patients, eight had increases in TSH above normal (three with TSH > 10 μU/liter, one with TSH of 32 μU/liter). Six weeks after mifepristone discontinuation, both HDL-C and thyroid function tests reverted to baseline levels.

**Discussion**

Cushing’s syndrome is a complex endocrine condition with serious sequelae, including cardiovascular mortality, fractures, proximal myopathy, insulin-resistant hyperglycemia, and neuropsychiatric and neurocognitive disorders (35, 36). Transsphenoidal pituitary surgery with adenoma resection is initially successful in 65–90% of patients with ACTH-secreting microadenomas when performed by ex-
pert surgeons, but approximately 20–25% have persistent hypercortisolism or recurrence postoperatively; cure rates are lower and recurrence rates are higher for macroadenomas (4). Morbidity and mortality in patients with CD are related to cortisol excess and rarely to the ACTH-secreting pituitary tumor mass. When surgery fails to reverse hypercortisolism, medical treatment can suppress cortisol overproduction and improve clinical manifestations. Bilateral adrenalectomy promptly resolves hypercortisolism but causes permanent adrenal cortical insufficiency mandating lifelong corticosteroid and mineralocorticoid replacement therapy. It may also decrease quality of life (5, 37) and can result in an enlargement of an ACTH-secreting pituitary tumor in 15–20% of cases (38). Patients with ectopic ACTH-secreting neoplasms or adrenocortical carcinoma often require control of hypercortisolism while waiting for definitive therapy or if definitive therapy is not feasible (39).

Mifepristone, a glucocorticoid receptor antagonist with binding affinity greater than dexamethasone and cortisol (10, 11), is rapidly absorbed orally, highly protein bound, and has a long half-life (40). The use of mifepristone in CS has been explored in case reports and/or small retrospective studies (9, 12–25). This is the largest prospective multicenter trial of mifepristone and demonstrates effectiveness in treating the clinical and metabolic derangements associated with hypercortisolism.

The two primary study endpoints were met: mifepristone significantly decreased AUC\textsubscript{glucose} during oGTT in patients with CS and T2DM or IGT and decreased DBP in a significant number of patients with CS and HTN. Significant decreases in FPG and HbA1c occurred in the C-DM cohort, and more than half the hypertensive patients in both groups had either an improvement in DBP or a reduction in antihypertensive medication. However, overall, there was no change in mean blood pressure from baseline to end of study.

As expected with a receptor-blocking strategy, ACTH and cortisol levels increased in patients with CD. Because high cortisol may not be completely inactivated by 11β-hydroxysteroid dehydrogenase type 2 in the kidney, excess cortisol may activate the mineralocorticoid receptor (41). This likely explains the increased blood pressure, hypokalemia, edema, and alkalosis seen in some patients; nine of the 12 patients with increased blood pressure were prescribed spironolactone.

Secondary endpoint results were noteworthy: mifepristone significantly decreased body weight, waist circumference, and body fat and increased insulin sensitivity. Clinically significant improvement was seen in 87% of patients, according to well-defined criteria used by the DRB. Moreover, 30 of the 34 patients who completed the 24-wk study elected to continue treatment with mifepristone.

Weight loss observed in the study may have been partially due to commonly experienced nausea and decreased appetite (see Supplemental Fig. 3) as well as to a direct result of glucocorticoid blockade. Moreover, it is not possible to discern whether these AEs result from medication or secondarily through a therapeutic effect of glucocorticoid withdrawal. Although clinically significant AI is a potential side effect of glucocorticoid receptor antagonism (9), it was uncommon during this study. Only two patients were reported to have AI; possible symptoms of AI including anorexia, nausea, lethargy, and dizziness occurred in five additional patients who also received glucocorticoids. It is important to note that cortisol elevations that occur in CD could be misleading and render the diagnosis of AI difficult. Without any available biochemical marker, these patients require close monitoring during treatment.

Decreased HDL-C and increased TSH were observed in some patients; these abnormalities resolved upon discontinuation of mifepristone. Because of its antiprogesterone effects, mifepristone has an impact on the endometrium characterized by thickening, with cystically dilated endometrial glands and features usually seen separately in normal proliferative and secretory endometrium (42). Ten women had AE of endometrial thickening, and abnormal vaginal bleeding occurred in five patients. An ongoing, long-term extension study will further characterize the safety profile of mifepristone in CS.

With the exception of a very aggressive tumor in one patient, there were no increases in tumor size, but it is important to note that the study duration was only 6 months. Data from longer-term use of mifepristone will be required to determine whether this risk is similar to that after bilateral adrenalectomy (38).

Limitations of the study include the lack of a placebo comparator group, the open-label design, exclusion of patients with de novo Cushing’s who were candidates for surgery, and the small number of adrenal cancer and ectopic ACTH cases. The dosing scheme allowing investigators to use their clinical judgment regarding increasing mifepristone based on benefit vs. tolerance produced heterogeneity in management, which is a limitation of the study. Similarly, interruptions or reduction in the dose of mifepristone to manage AE produced additional dosing pattern heterogeneity. An assessment of dose response overall was therefore not possible.

Glucocorticoid receptor antagonism with mifepristone may offer a new approach to control the clinical manifestations of endogenous hypercortisolism in patients who have not responded to multimodal therapies. Although the side effect profile over 6 months is well characterized and
manageable with additional medications, the long-term efficacy and safety remain to be determined, particularly with regard to the need for potassium supplementation and/or mineralocorticoid receptor blockade and endometrial monitoring. Because mifepristone does not decrease cortisol production, measurement of this hormone should not be performed during treatment; careful monitoring by clinicians familiar with the mechanism of action of this unique agent is essential. Long-term data are needed to further define the role of mifepristone in the medical treatment of CS.

Acknowledgments

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This study was supported by Corcept Therapeutics.

All drafts of the manuscript were written and reviewed by all the authors.

Disclosure Summary: B.M.K.B., J.W.F., and M.E.M. are consultants to Corcept Therapeutics, Inc. B.M.K.B., J.W.F., M.E.M., M.F., and D.E.S. served as investigators on research grants to their institutions from Corcept Therapeutics, Inc. C.G. is an employee of Corcept Therapeutics, Inc. B.M.K.B., J.W.F., and M.F. are consultants to and serve as investigators on research grants to their institutions from Novartis.

References

INDICATIONS AND USAGE

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.

Important Limitations of Use

• Do not use for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing’s syndrome.

DOSE AND ADMINISTRATION

• Administer once daily orally with a meal (2).
• The recommended starting dose is 300 mg once daily (2).
• Renal impairment: do not exceed 600 mg once daily.
• Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily.

Based on clinical response and tolerability, the dose may be increased in 300 mg increments to a maximum of 1200 mg once daily. Do not exceed 20 mg/kg per day (2).

DOSE FORMS AND STRENGTHS

• 300 mg tablet

CONTRAINDICATIONS

• Pregnancy (4.1, 8.1)
• Use of simvastatin or lovastatin and CYP3A substrates with narrow therapeutic range (4.2)
• Concurrent long-term corticosteroid use (4.3)
• Women with history of unexplained vaginal bleeding (4.4)
• Women with endometrial hyperplasia with atypia or endometrial carcinoma (4.4)

ADVERSE REACTIONS

Most common adverse reactions in Cushing’s syndrome (≥ 20%): nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, endometrial hypertrophy.

WARNINGS AND PRECAUTIONS

• Adrenal insufficiency: Patients should be closely monitored for signs and symptoms of adrenal insufficiency (5.1).
• Hypokalemia: Hypokalemia should be corrected prior to treatment and monitored for during treatment (5.2).
• Vaginal bleeding and endometrial changes: Women may experience endometrial thickening or unexpected vaginal bleeding. Use with caution if patient also has a hemorrhagic disorder or is on anti-coagulant therapy (5.3).
• QT interval prolongation: Avoid use with QT interval prolonging drugs, or in patients with potassium channel variants resulting in a long QT interval (5.4).
• Use of Strong CYP3A Inhibitors: Concomitant use may increase mifepristone plasma levels significantly. Use only when necessary and limit mifepristone dose to 300 mg (5.6).

USE IN SPECIFIC POPULATIONS

• Nursing mothers: Discontinue drug or discontinue nursing (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: JUN 2013
Korlym® (mifepristone) 300 mg Tablets for oral use

1 INDICATIONS AND USAGE

Korlym (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia in non-insulin-dependent diabetic females of reproductive potential.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

The recommended starting dose is 300 mg orally once daily. Korlym must be given as a single daily dose. Korlym should always be taken with a meal. Patients should swallow the tablet whole. Do not split, crush, or chew tablets.

Dosing and titration

The daily dose of Korlym may be increased in 300 mg increments. The dose of Korlym may be increased to a maximum of 1200 mg once daily but should not exceed 20 mg/kg per day. Increases in dose should not occur more frequently than once every 2-4 weeks. Decisions about dose increases should be based on a clinical assessment of tolerability and degree of improvement in Cushing’s syndrome manifestations. Changes in glucose control, anti-diabetic medication requirements, insulin levels, and psychiatric symptoms may provide an early assessment of response (within 6 weeks) and may help guide early dose titration. Improvements in cushingoid appearance, acne, hirsutism, strie, and body weight occur over a longer period of time and, along with measures of glucose control, may be used to determine dose changes beyond the first 2 months of therapy. Careful and gradual titration of Korlym accompanied by monitoring for recognized adverse reactions (See Warnings and Precautions 5.1 and 5.2) may reduce the risk of severe adverse reactions. Dose reduction or even dose discontinuation may be needed in some clinical situations. If Korlym treatment is interrupted, it should be reintitated at the lowest dose (300 mg). If treatment was interrupted because of adverse reactions, the titration should aim for a dose lower than the one that resulted in treatment interruption.

2.2 Dosing in Renal Impairment

No change in initial dose of Korlym is required in renal impairment. The maximum dose should be limited to 600 mg. [See Renal Impairment (8.6) and Clinical Pharmacology (12.3)].

2.3 Dosing in Hepatic Impairment

No change in the initial dose of Korlym is required in mild to moderate hepatic impairment. The maximum dose should be limited to 600 mg. Korlym should not be used in severe hepatic impairment. [See Hepatic Impairment (8.7) and Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

Korlym is supplied as a light yellow to yellow oval-shaped tablet debossed with “Concept” on one side and “300” on the other. Each tablet contains 300 mg of mifepristone. The tablets are scored.

4 CONTRAINDICATIONS

4.1 Pregnancy

Korlym is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with Korlym or if treatment is interrupted for more than 14 days in females of reproductive potential. Nonhormonal contraceptives should be used during and for one month after stopping treatment in all women of reproductive potential. [See Use in Specific Populations 8.8].

4.2 Drugs Metabolized by CYP3A

Korlym is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, diltiazem, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, due to an increased risk of adverse events. [See Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

4.3 Corticosteroid Therapy Required for Lifesaving Purposes

Korlym is contraindicated in patients who require concomitant treatment with systemic corticosteroids for serious medical conditions or illnesses (e.g., immunosuppression after organ transplantation) because Korlym antagonizes the effect of glucocorticoids.

4.4 Women with Risk of Vaginal Bleeding or Endometrial Changes

Korlym is contraindicated in the following:

- Women with a history of unexplained vaginal bleeding
- Women with endometrial hyperplasia with atypia or endometrial carcinoma

4.5 Known Hypersensitivity to Mifepristone

Korlym is contraindicated in patients with prior hypersensitivity reactions to mifepristone or to any of the product components.

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Insufficiency

Patients receiving mifepristone may experience adrenal insufficiency. Because serum cortisol levels remain elevated and may even increase during treatment with Korlym, serum cortisol levels do not provide an accurate assessment of hypocortisolism in patients receiving Korlym. Patients should be closely monitored for signs and symptoms of adrenal insufficiency, including weakness, nausea, increased fatigue, hypotension, and hypoglycemia. If adrenal insufficiency is suspected, discontinue treatment with Korlym immediately and administer glucocorticoids without delay. High doses of supplemental glucocorticoids may be needed to overcome the glucocorticoid receptor blockade produced by mifepristone. Factors considered in deciding on the duration of glucocorticoid treatment should include the long half-life of mifepristone (85 hours).

5.2 Hypokalemia

In a study of patients with Cushing’s syndrome, hypokalemia was observed in 44% of subjects during treatment with Korlym. Hypokalemia should be corrected prior to initiating Korlym. During Korlym administration, serum potassium should be measured 1 to 2 weeks after starting or increasing the dose of Korlym and periodically thereafter. Hypokalemia can occur at any time during Korlym treatment. Mifepristone-induced hypokalemia should be treated with intravenous or oral potassium supplementation based on event severity. If hypokalemia persists in spite of potassium supplementation, consider adding mineralocorticoid antagonists.

5.3 Vaginal Bleeding and Endometrial Changes

Being an antagonist of the progesterone receptor, mifepristone promotes unopposed endometrial proliferation that may result in endometrium thickening, cystic dilation of endometrial glands, and vaginal bleeding. Korlym should be used with caution in women who have hemorrhagic disorders or are receiving concurrent anticoagulant therapy. Women who experience vaginal bleeding during Korlym treatment should be referred to a gynecologist for further evaluation.

5.4 QT Interval Prolongation

Mifepristone and its metabolites block IfK. Korlym prolongs the QTc interval in a dose-related manner. There is little or no experience with high exposure, concomitant dosing with other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval. [See Warnings & Precautions 5.6] To minimize risk, the lowest effective dose should always be used.

5.5 Exacerbation/Deterioration of Conditions Treated with Corticosteroids

Use of Korlym in patients who receive corticosteroids for other conditions (e.g., autoimmune disorders) may lead to exacerbation or deterioration of such conditions, as Korlym antagonizes the desired effects of glucocorticoid in these clinical settings. For medical conditions in which chronic corticosteroid therapy is lifesaving (e.g., immunosuppression in organ transplantation), Korlym is contraindicated. [See Contraindications (4.3)].

5.6 Use of Strong CYP3A Inhibitors

Korlym should be used with extreme caution in patients taking ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, rifampin, rifabutin, and azole antifungal agents, as they may significantly increase the plasma levels of mifepristone and increase the risk of adverse effects including adrenal insufficiency, amenorrhea, and withdrawal breast pain.

5.7 Pneumocystis jiroveci Infection

Patients with endogenous Cushing’s syndrome are at risk for opportunistic infections such as Pneumocystis jiroveci pneumonia during Korlym treatment. Patients may present with respiratory distress shortly after initiation of Korlym. Appropriate diagnostic tests should be undertaken and treatment for Pneumocystis jiroveci should be considered.

5.8 Potential Effects of Hypercortisolism

Korlym does not reduce serum cortisol levels. Elevated cortisol levels may activate mineralocorticoid receptors which are also expressed in cardiac tissues. Caution should be used in patients with underlying heart conditions including heart failure and coronary vascular disease.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Safety data on the use of Korlym are available from 50 patients with Cushing’s syndrome enrolled in an uncontrolled, open-label, multi-center trial (Study 400). Forty-three patients had Cushing’s disease and all except one had previously undergone pituitary surgery. Four patients had ectopic ACTH secretion, and three had adrenal carcinoma. Patients were treated for up to 24 weeks. A dose of 300 mg per day was administered for the initial 14 days; thereafter, the dose could be escalated in increments of 300 mg per day based on assessments of tolerability and clinical response. Doses were escalated up to 900 mg per day for patients <60 kg, or 1200 mg per day for patients >60 kg. The most frequently reported adverse reactions (reported in ≥20% of patients, regardless of relationship to Korlym) were nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hyperthrophy. Drug-related adverse events resulted in dose interruption or reduction in study drug in 40% of patients.
The adverse reactions that occurred in ≥10% of the Cushing’s syndrome patients receiving Korlym, regardless of relationship to Korlym, are shown in Table 1.

Table 1. Treatment Emergent Adverse Events Occurring in ≥10% of Cushing’s Syndrome Patients Receiving Korlym

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Percent (% of Patients Reporting Event (n = 50))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>48</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>18</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
</tr>
<tr>
<td>General disorders and administration/site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>26</td>
</tr>
<tr>
<td>Pain</td>
<td>14</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>44</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>30</td>
</tr>
<tr>
<td>Back pain</td>
<td>16</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>24</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>38^a</td>
</tr>
<tr>
<td>Endometrial hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>10</td>
</tr>
</tbody>
</table>

*The denominator was 26 females who had baseline and end-of-trial transvaginal ultrasound.

6.2 Laboratory Tests

Reductions in high density lipoprotein cholesterol (HDLC) levels have been observed following treatment with Korlym. In study subjects that experienced declines in HDLC, levels returned to baseline following discontinuation of drug. The clinical significance of the treatment-related reduction in HDLC levels in patients with Cushing’s syndrome is not known.

In a study of patients with Cushing’s syndrome, hypokalemia was observed in 44% of subjects during treatment with Korlym. In these cases, hypokalemia responded to treatment with potassium supplementation and/or mineralocorticoid antagonist therapy (e.g., spironolactone). Hypokalemia should be corrected prior to initiating Korlym. [See Warnings and Precautions (5.2)].

Elevations of thyroid-stimulating hormone (TSH) were seen in subjects treated with Korlym. Of the 42 subjects with detectable TSH at baseline, eight (19%) had increases in TSH above the normal range, while remaining asymptomatic. The TSH levels returned to normal in most patients without intervention when Korlym was discontinued at the end of the study.

6.3 Vaginal Bleeding and Endometrial Changes

In Study 400, the thickness of the endometrium increased from a mean of 6.14 mm at baseline (n=23) to 15.7 mm at end of trial (n=18) in premenopausal women; in postmenopausal women the increase was from 2.75 mm (n=6) to 7.35 mm (n=8). Endometrial thickness above the upper limit of normal was reported in 10/26 females who had baseline and end-of-trial transvaginal ultrasound (38%). The endometrial thickness returned to the normal range in 3 out of 10 patients 6 weeks after treatment cessation at the end of the study. Vaginal bleeding occurred in 5 out of 35 females (14%). Two of five subjects with vaginal bleeding had normal endometrial thickness. Endometrial biopsies were performed in six patients; five of these patients had endometrial thickening. No endometrial carcinoma was detected in the sampled cases.

6.4 Additional Data from Clinical Trials

The following are adverse events that were reported in Study 400 at frequencies of ≥5% to 10%, and may be related to Korlym’s mechanism of action:

- Gastrointestinal disorders: gastrointestinal reflux, abdominal pain
- General disorders and administration site conditions: asthenia, malaise, edema, pitting edema, thirst
- Investigations: blood triglycerides increased
- Metabolism and nutrition disorders: hypoglycemia
- Musculoskeletal and connective tissue disorders: musculoskeletal pain
- Psychiatric disorders: insomnia
- Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia

6.4.1 Adrenal Insufficiency

Adrenal insufficiency was reported in two subjects (4%) in Study 400. The most typical symptoms of adrenal insufficiency were nausea and decreased appetite. No hypotension or hypoglycemia was reported during the events. Adrenal insufficiency resolved in both cases with Korlym interruption and/or dexamethasone administration.

6.4.2 Rash

Generalized, maculo-papular rash was reported in 2 subjects (4%) in Study 400. Two additional subjects developed pruritis (4%). None resulted in discontinuation of Korlym, and all the events resolved by the end of the study.

7 DRUG INTERACTIONS

Based on the long terminal half-life of mifepristone after reaching steady state, at least 2 weeks should elapse after cessation of Korlym before initiating or increasing the dose of any interacting concomitant medication.

7.1 Drugs Metabolized by CYP3A

Because Korlym is an inhibitor of CYP3A, concurrent use of Korlym with a drug whose metabolism is largely or solely mediated by CYP3A is likely to result in increased plasma concentrations of the drug. Discontinuation or dose reduction of such medications may be necessary with Korlym co-administration.

Korlym increased the exposure to simvastatin and simvastatin acid significantly in healthy subjects. Concomitant use of simvastatin or lovastatin is contraindicated because of the increased risk of myopathy and rhabdomyolysis. [See Contraindications (4.2), Clinical Pharmacology (12.3)].

The exposure of other substrates of CYP3A with narrow therapeutic ranges, such as cyclosporine, dihydropyridine calcium blockers, and sirolimus, may be increased by concomitant administration with Korlym. Therefore, the concomitant use of such CYP3A substrates with Korlym is contraindicated. [See Contraindications (4.2)]

Other drugs with similar high first pass metabolism in which CYP3A is the primary route of metabolism should be used with extreme caution if co-administered with Korlym. The lowest possible dose and/or a decreased frequency of dosing must be used with therapeutic drug monitoring when possible. Use of alternative drugs without these metabolic characteristics is advised when possible with concomitant Korlym.

If drugs that undergo low first pass metabolism by CYP3A or drugs in which CYP3A is not the major metabolic route are co-administered with Korlym, use the lowest dose of concomitant medication necessary, with appropriate monitoring and follow-up. [See Clinical Pharmacology (12.3)].

7.2 CYP3A Inhibitors

Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of Korlym may be required.

Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, neflinavir, indinavir, atazanavir, and fosamprenavir, have been shown to increase the plasma concentrations of mifepristone, mifepristone acid, and/or mifepristone metabolites. Therefore, the concomitant use of such CYP3A substrates with Korlym is contraindicated. [See Contraindications (4.2)].

Other moderate inhibitors of CYP3A, such as amnepirin, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, or verapamil, should be used with caution when administered in combination with Korlym.

The benefit of concomitant use of these agents should be carefully weighed against the potential risks. The dose of Korlym should be limited to 300 mg and used only when necessary. [See Warnings and Precautions (5.6)].

Moderate inhibitors of CYP3A, such as amnepirin, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, or verapamil, should be used with caution when administered in combination with Korlym.

7.3 CYP3A Inducers

No medications that induce CYP3A have been studied when co-administered with Korlym. Avoid co-administration of Korlym and CYP3A inducers such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John’s wort.

7.4 Drugs Metabolized by CYP2C8/2C9

Because Korlym is an inhibitor of CYP2C8/2C9, concurrent use of Korlym with a drug whose metabolism is largely or solely mediated by CYP2C8/2C9 is likely to result in increased plasma concentrations of the drug. Korlym significantly increased exposure of fluvoxatin, a typical CYP2C8/2C9 substrate, in healthy volunteers. When given concomitantly with Korlym, drugs that are substrates of CYP2C8/2C9 (including non-steroidal anti-inflammatory drugs, warfarin, and retapin) should be used at the smallest recommended doses, and patients should be closely monitored for adverse effects. [See Clinical Pharmacology (12.3)].

7.5 Drugs Metabolized by CYP2B6

Mifepristone is an inhibitor of CYP2B6 and may cause significant increases in exposure of drugs that are metabolized by CYP2B6 such as bupropion and efavirenz. Since no studies have been conducted to evaluate the effect of mifepristone on substrates of CYP2B6, the concomitant use of bupropion and efavirenz should be undertaken with caution. [See Clinical Pharmacology (12.3)].

7.6 Use of Hormonal Contraceptives

Mifepristone is a progesterone receptor antagonist and will interfere with the effectiveness of hormonal contraceptives. Therefore, non-hormonal contraceptive methods should be used.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category X

Korlym is contraindicated in pregnancy. Korlym can cause fetal harm when administered to a pregnant woman because the use of Korlym results in pregnancy loss. The inhibition of both endogenous and exogenous progesterone by mifepristone at the progestosterone receptor results in pregnancy loss. If Korlym is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. [See Contraindications (4.1)].

Human Data

In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area) were carried out. Because of the anti-progestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at less than human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or
mifepristone is present in human milk of women taking the drug. Because of the potential for serious adverse reactions in nursing infants from Korlym, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness of Korlym in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies with Korlym did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger people.

8.6 Renal Impairment
The maximum dose should not exceed 600 mg per day in renally impaired patients.

[See Clinical Pharmacology (12.3)]

8.7 Hepatic Impairment
In patients with mild to moderate hepatic impairment, the maximum dose should not exceed 600 mg per day. The pharmacokinetics of mifepristone in patients with severe hepatic impairment has not been studied, and Korlym should not be used in these patients.

[See Clinical Pharmacology (12.3)]

8.8 Females of Reproductive Potential
Due to its anti-progestational activity, Korlym causes pregnancy loss. Exclude pregnancy before the initiation of treatment with Korlym or if treatment is interrupted for more than 14 days in females of reproductive potential. Recommend contraception for the duration of treatment and for one month after stopping treatment using a non-hormonal medically acceptable method of contraception. If the patient has had surgical sterilization, no additional contraception is needed.

10 OVERDOSAGE
There is no experience with overdose of Korlym.

11 DESCRIPTION
Korlym (mifepristone) is a cortisol receptor blocker for oral administration. The chemical name of mifepristone is 115-[4-dimethylaminophenyl]-17β-hydroxy-17α-[1-propynyl]-estra-4,9-dien-3-one. The chemical formula is C23H29NO2; the molecular weight is 429.60, and the structural formula is:

![Chemical Structure of Mifepristone]

Mifepristone demonstrates a pH-related solubility profile. The greatest solubility is achieved in acidic media (~ 25 mg/mL at pH 1.5) and solubility declines rapidly as the pH is increased. At pH values above 2.5 the solubility of mifepristone is less than 1 mg/mL.

Each Korlym tablet for oral use contains 300 mg of mifepristone. The inactive ingredients of Korlym tablets are silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polyethylene 80, and FD&C yellow 6 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Mifepristone is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses. Mifepristone has high affinity for the GR-II receptor but little affinity for the GR-I (MR, mineralocorticoid receptor). In addition, mifepristone appears to have little or no affinity for estrogen, muscarinic, histaminic, or monoamine receptors.

12.2 Pharmacodynamics
Because mifepristone acts at the receptor level to block the effects of cortisol, 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 the three active metabolites have greater affinity for the glucocorticoid receptor (100%, 61%, 48%, and 45%, respectively) than either dexemethasone (23%) or cortisol (9%).

12.3 Pharmacokinetics

Absorption
Following oral administration, time to peak plasma concentrations of mifepristone occurred between 1 and 2 hours following single dose, and between 1 and 4 hours following multiple doses of 600 mg of Korlym in healthy volunteers. Mean plasma concentrations of three active metabolites of mifepristone peak between 2 and 8 hours after multiple doses of 600 mg/day, and the combined concentrations of the metabolites exceed that of the parent mifepristone. Exposure to mifepristone is substantially less than dose proportional. Time to steady state is within 2 weeks, and the mean (SD) half-life of the parent mifepristone was 85 (61) hours following multiple doses of 600 mg/day of Korlym.

Studies evaluating the effects of food on the pharmacokinetics of Korlym demonstrate a significant increase in plasma levels of mifepristone when dosed with food. To achieve consistent plasma drug concentrations, patients should be instructed to always take their medication with meals.

Distribution
Mifepristone is highly bound to alpha-1-acid glycoprotein (AAG) and approaches saturation at doses of 100 mg (2.5 µM) or more. Mifepristone and its metabolites also bind to albumin and are distributed to other tissues, including the central nervous system (CNS). As determined in vitro by equilibrium dialysis, binding of mifepristone and its three active metabolites to human plasma proteins was concentration-dependent. Binding was approximately 99.2% for mifepristone, and ranged from 96.1 to 98.9% for the three active metabolites at clinically relevant concentrations.

Metabolism
Cyclochrome P450 3A4 (CYP3A4) has been shown to be involved in mifepristone metabolism in human liver microsomes. Two of the known active metabolites are the product of demethylation (one monodemethylated and one di-demethylated), while a third active metabolite results from hydroxylation (monohydroxylated).

Elimination and Excretion
Excretion is primarily (approximately 90%) via the fecal route.

Specific Populations

Renal Impairment
The pharmacokinetics of mifepristone in subjects with severe renal impairment (creatinine clearance (CrCl) < 30 mL/min, but not on dialysis) was evaluated following multiple doses of 1200 mg Korlym for 7 days. Mean exposure to mifepristone increased 31%, with similar or smaller increases in metabolite exposure as compared to subjects with normal renal function (CrCl ≥ 90 mL/min). There was large variability in the exposure of mifepristone and its metabolites in subjects with severe renal impairment as compared to subjects with normal renal function (geometric least square mean ratio [CI] for AUC of mifepristone: 1.21 [0.71-2.06]; metabolite 1: 1.43 [0.84-2.44]; metabolite 2: 1.18 [0.64-2.17] and metabolite 3: 1.19 [0.71-1.99]. No change in the initial dose of Korlym is needed for renal impairment; the maximum dose should not exceed 600 mg per day.

Hepatic Impairment
The pharmacokinetics of mifepristone in subjects with moderate hepatic impairment (Child-Pugh Class B) was evaluated in a single- and multiple-dose study (600 mg for 7 days). The pharmacokinetics in subjects with moderate hepatic impairment was similar to those with normal hepatic function. There was large variability in the exposure of mifepristone and its metabolites in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function (geometric least square mean ratio [CI] for AUC of mifepristone: 1.02 [0.59-1.76]; metabolite 1: 1.05 [0.52-2.1]; metabolite 2: 1.37 [0.71-2.62] and metabolite 3: 0.62 [0.33-1.16]). Due to limited information on safety in patients with mild-to-moderate hepatic impairment, the maximum dose should not exceed 600 mg per day.

The pharmacokinetics of mifepristone in patients with severe hepatic disease has not been studied. Korlym is not recommended in patients with severe hepatic disease.

Drug-Drug Interactions

In Vitro Assessment of Drug Interactions
In vitro studies indicate a potential for CYP-mediated drug interactions by mifepristone and/or its metabolites with substrates of CYP2A6, CYP2C8/29, CYP2C19, CYP3A4, CYP1A2, CYP2B6, CYP2D6, and CYP2E1. In vitro studies also indicated an interaction potential for drug transport mediated by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In vitro studies indicate mifepristone metabolism is mediated by CYP3A, and that mifepristone also inhibits and induces CYP3A.

In Vivo Assessment of Drug Interactions (see Table 2)

Table 2. Summary Table of Korlym Drug-Drug Interaction Effects

<table>
<thead>
<tr>
<th>Dosing of Mifepristone</th>
<th>Coadministered Drug</th>
<th>Dosing of Mifepristone</th>
<th>Geometric Mean Ratio (analyte ratio with/without drug coadministration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200 mg once daily for 10 days</td>
<td>simvastatin¹</td>
<td>80 mg single dose</td>
<td>simvastatin acid</td>
</tr>
<tr>
<td></td>
<td>15.70</td>
<td>18.20</td>
<td>10.40</td>
</tr>
<tr>
<td>1200 mg once daily for 7 days</td>
<td>alprazolam²</td>
<td>1 mg single dose</td>
<td>alprazolam 4-hydroxy-alprazolam</td>
</tr>
<tr>
<td></td>
<td>0.81</td>
<td>0.39</td>
<td>1.90</td>
</tr>
<tr>
<td>1200 mg once daily for 7 days</td>
<td>fluvastatin³</td>
<td>40 mg single dose</td>
<td>fluvastatin</td>
</tr>
<tr>
<td></td>
<td>1.64</td>
<td>1.04</td>
<td>1.64</td>
</tr>
</tbody>
</table>

¹ Simvastatin 40 mg dose used as reference for the comparison. Result could be representative of other oral drugs with CYP3A metabolism and high first pass effect: cyclosporine, midazolam, triazolam, pemoline, sildenafil, sirolimus, and tacrolimus

² Result could be representative of other oral drugs with CYP3A metabolism and low first pass effect, clinical significance of any interaction will depend on the therapeutic margin of the drug

³ Plasma digoxin concentration should be measured after 1 to 2 weeks of concomitant use and following usual clinical practice at appropriate intervals thereafter

No effect: 90% CI within range 0.80 – 1.25

*No effect = 90% CI within range 0.80 – 1.25

¹ Simvastatin 40 mg dose used as reference for the comparison. Result could be representative of other oral drugs with CYP3A metabolism and high first pass effect: cyclosporine, midazolam, triazolam, pemoline, sildenafil, sirolimus, and tacrolimus

² Result could be representative of other oral drugs with CYP3A metabolism and low first pass effect. Clinical significance of any interaction will depend on the therapeutic margin of the drug

³ Result could be representative of other oral drugs with CYP3A metabolism

⁴ Plasma digoxin concentration should be measured after 1 to 2 weeks of concomitant use and following usual clinical practice at appropriate intervals thereafter

⁵ Result could be representative of other oral drugs with CYP3A metabolism

⁶ Plasma digoxin concentration should be measured after 1 to 2 weeks of concomitant use and following usual clinical practice at appropriate intervals thereafter
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Mifepristone was evaluated for carcinogenicity potential in rats and mice. Rats were dosed for up to two years at doses of 5, 25, and 125 mg/kg of mifepristone. The high dose was the maximum tolerated dose, but exposure at all doses was below exposure at the maximum clinical dose based on AUC comparison. Female rats had a statistically significant increase in follicular cell adenomas/carcinomas and liver adenomas. It is plausible that these tumors are due to drug-induced enzyme metabolism, a mechanism not considered clinically relevant, but studies confirming this mechanism were not conducted with mifepristone. Mice were also tested for up to 2 years at mifepristone doses up to the maximum tolerated dose of 125 mg/kg, which provided exposure below the maximum clinical dose based on AUC. No drug-related tumors were seen in mice.

Mifepristone was not genotoxic in a battery of bacterial, yeast, and mammalian in vitro assays, and an in vivo micronucleus study in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of adult rats at a dose of 0.3 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area). The pharmacological activity of mifepristone disrupts the estrus cycle of adult rats at a dose of 1 mg/kg every other day to neonatal rats resulted in potentially adverse fertility effects, including ovuidct and ovary malformations in females, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency.

14 CLINICAL STUDIES

14.1 Cushing’s Syndrome
An uncontrolled, open-label, 24-week, multicenter clinical study was conducted to evaluate the safety and efficacy of Korlym in the treatment of endogenous Cushing’s syndrome. The study enrolled 50 subjects with clinical and biochemical evidence of hypercortisolism despite prior surgical treatment and radiotherapy. The reasons for medical treatment were not adversely affect future reproductive function in males or females, although the onset of puberty was slightly premature in female patients. Dosed for 300 mg once a day, the study protocol allowed an increase in dose to 600 mg after 2 weeks, and then by additional 300 mg increments every 4 weeks to a maximum of 900 mg per day for patients <60 kg, or 1200 mg per day for patients ≥60 kg, based on clinical tolerance and clinical response.

Results in the diabetes cohort
Patients in the diabetes cohort underwent standard oral glucose tolerance tests at baseline and periodically during the clinical study. Anti-diabetic medications were allowed but had to be kept stable during the trial and patients had to be on stable anti-diabetic regimens prior to enrollment. The primary efficacy analysis for the diabetes cohort was an analysis of responders. A responder was defined as a patient who had a ≥25% reduction from baseline in glucose AUC. The primary efficacy analysis was conducted in the modified intent-to-treat population (n=25) as all patients who received a minimum of 30 days on Korlym. Fifteen of 25 patients (60%) were treatment responders (95% CI: 39%, 78%,). Mean HbA1c was 7.4% in the 24 patients with HbA1c values at baseline and Week 24. For these 24 patients, mean reduction in HbA1c was 1.1% (95% CI: -1.6, -0.7) from baseline to the end of the trial. Seventeen of 24 patients had above normal HbA1c levels at baseline, ranging between 6.7% and 10.4%; all of these patients had reductions in HbA1c by the end of the study (range -0.4 to -4.4%) and eight of 14 patients (57%) normalized HbA1c levels at trial end. Antidiabetic medications were reduced in 7 of the 15 DM subjects taking antidiabetic medication and remained constant in the others.

Results in the hypertension cohort
There were no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21).

Signs and symptoms of Cushing’s syndrome in both cohorts
Individual patients showed varying degrees of improvement in Cushing’s syndrome manifestations such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight. Because of the variability in clinical presentation and variability of response in this open label trial, it is uncertain whether these changes could be ascribed to the effects of Korlym.

16 HOW SUPPLIED/STORAGE AND HANDLING
Korlym is supplied as a light yellow to yellow, film-coated, oval-shaped tablet debossed with “Korlym” on one side and “300” on the other. Each tablet contains 300 mg of mifepristone. Korlym tablets are available in bottles of 28 tablets (NDC 76346-073-01) and bottles of 280 tablets (NDC 76346-073-02). Store at controlled room temperature, 25 °C (77 °F); excursions permitted to 15 to 30 °C (59 – 86 °F). [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION
As a part of patient counseling, doctors must review the Korlym Medication Guide with each patient. [See FDA-Approved Medication Guide (17.3)]

17.1 Importance of Preventing Pregnancy
• Advise patients that Korlym will cause termination of pregnancy. Korlym is contra indicated in pregnant patients.
• Counsel females of reproductive potential regarding pregnancy prevention and planning with a non-hormonal contraceptive prior to use of Korlym and up to one month after the end of treatment.
• Instruct patients to contact their physician immediately if they suspect or confirm they are pregnant.

17.3 FDA-Approved Medication Guide

Medication Guide
Korlym® (COR-lim) (mifepristone) tablets
Read this Medication Guide before you start taking Korlym and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about Korlym? Korlym can cause serious side effects, including:

• Loss of a pregnancy. Women who can become pregnant must:
  – have a negative pregnancy test before starting Korlym
  – have a negative pregnancy test before restarting Korlym if you stop taking it for more than 14 days
  – use a non-hormonal form of birth control while taking Korlym and for 1 month after stopping Korlym. Talk to your doctor about how to prevent pregnancy. Tell your doctor right away if you think you may be pregnant.

What is Korlym? Korlym is a prescription medicine used to treat high blood sugar (hyperglycemia) caused by high cortisol levels in the blood (hypercortisolism) in adults with endogenous Cushing’s syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or cannot have surgery.

Korlym is not for people who have type 2 diabetes mellitus not caused by Cushing’s syndrome.

It is not known if Korlym is safe and effective in children.

Who should not take Korlym? Do not take Korlym if you:

• are pregnant. See “What is the most important information I should know about Korlym?”

• are taking:
  – simvastatin (Zocor®), Vitoryn®, Juvisync®, Simcor®
  – lovastatin (Mevacor®, Altoprev®, Advisor®)
  – cyclosporine (Gengraf®, Neoral®, Restasis®, Sandimmune®)
  – dihydroergotamine (Migranal®)
  – ergotamine (Ergomar®, Migrergot®)
  – fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Sublingual Preservative Free®, Subsys®)
  – pimozide (Orap®)
  – quinidine (Neudexta®)
  – sirolimus (Rapamune®, Torisel®)
  – tacrolimus (Prograf®, Protopic®)
  – must take corticosteroid medicines for other serious medical problems
  – a woman who still has her uterus (womb) and have:
    – unexplained bleeding from your vagina
    – changes in the cells lining your uterus (endometrial hyperplasia) or cancer of the lining of your uterus (endometrial cancer)

• are allergic to mifepristone or any of the ingredients in Korlym. See the end of this Medication Guide for a complete list of ingredients in Korlym.

Talk to your doctor before taking Korlym if you have any of these conditions.

What should I tell my doctor before taking Korlym? Before taking Korlym, tell your doctor if you:

• have low potassium in your blood (hypokalemia)
• have or have had a bleeding problem or are taking medicines to thin your blood
• have or have had heart problems
• have had an organ transplant
• have been taking medicines called corticosteroids (cortisone, dexamethasone, methylprednisolone, prednisolone, prednisone)
• are breastfeeding or plan to breastfeed. Korlym passes into your breast milk and may harm your baby. You and your doctor should decide if you will take Korlym or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

Using Korlym with certain other medicines can affect each other. Using Korlym with other medicines can cause serious side effects.
Especially tell your doctor if you take:
- medicines to treat:
  - fungal infections (such as ketoconazole)
  - depression
  - HIV infection
  - Hepatitis C infection
  - certain bacterial infections
- steroid medicines such as prednisone
- thyroid hormones

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist.

How should I take Korlym?
- Take Korlym exactly as your doctor tells you.
- Your doctor may change your dose if needed.
- Korlym is usually taken 1 time each day.
- Take Korlym with food.
- Swallow Korlym whole. Do not split, crush or chew Korlym tablets. If you cannot swallow Korlym tablets whole, tell your doctor.

What should I avoid while taking Korlym?
You should not drink grapefruit juice while you take Korlym. Grapefruit juice may increase the amount of Korlym in your blood and increase your chance of having side effects.

What are the possible side effects of Korlym?
Korlym can cause serious side effects including:
- See “What is the most important information I should know about Korlym?”
- reduced effects of adrenal hormones (adrenal insufficiency). Korlym stops an adrenal hormone in your body called cortisol from working. Tell your doctor right away if you have any symptoms of adrenal insufficiency. Symptoms may include:
  - unusual tiredness or weakness
  - nausea
  - fatigue
  - low blood pressure (hypotension)
  - low blood sugar (hyperglycemia)
- low blood potassium (hypokalemia). Your doctor should check the level of potassium in your blood before you start taking Korlym and while you take it. Tell your doctor if you have any signs of low potassium. Signs may include:
  - muscle weakness, aches, or cramps
  - abnormal or irregular heartbeats (palpitations)
- bleeding from the vagina. Korlym may cause the lining of your uterus to become thick and may cause your uterus to bleed. Tell your doctor right away about any bleeding from your vagina that is not normal for you.
- problems with the electrical system of your heart (QT interval prolongation).
- worsening of symptoms of other medical problems that are treated with corticosteroids when you take corticosteroids and Korlym at the same time.

The most common side effects of Korlym include:
- nausea
- fatigue
- headache
- low potassium in your blood
- pain in your arms and legs (arthralgia)
- vomiting
- swelling of your arms and legs (peripheral edema)
- high blood pressure
- dizziness
- decreased appetite
- thickening of the lining of the uterus (endometrial hypertrophy)

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Korlym. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.