FINDING THE OPTIMAL DOSE OF KORLYM® (mifepristone)

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.

IMPORTANT SAFETY INFORMATION

WARNING: TERMINATION OF PREGNANCY

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

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Korlym®
mifepristone
300 mg Tablets

3 STEPS TO FINDING THE OPTIMAL KORLYM DOSE

1 EVALUATE
baseline parameters, such as[1]:

Hyperglycemia/ T2DM	**Weight**
Glucose-control medications	**Psychiatric symptoms**

2 MONITOR
the following[1]

- ☑ **BLOOD POTASSIUM**
- ☑ **BLOOD SUGAR**
- ☑ **BLOOD PRESSURE**

Measurement of cortisol levels is not an effective measure of treatment response

3 REASSESS Korlym dose[1]

INCREASE	Patient has not yet achieved sufficient clinical improvement
MAINTAIN	Patient has achieved sufficient clinical improvement
DECREASE	Patient is unable to tolerate current dose
STOP	Patient experiences a serious adverse effect

BEFORE STARTING KORLYM[1]

- **Exclude** pregnancy. Korlym should not be taken by women who are pregnant, may become pregnant, or those who are breastfeeding or plan to breastfeed
- **Rule out** contraindications
- **Check**
  - Blood potassium levels (correct if needed)
  - Drug–drug interactions
- **Evaluate baseline parameters**
  - Hyperglycemia/T2DM
  - Glucose-control medications
  - Weight
  - Psychiatric symptoms
- **Inform**
  - Patient of cortisol withdrawal side effects (nausea, fatigue, headache, and reduction in glucose levels)
  - Comanaging healthcare providers about side effects that may occur during treatment
- **Discuss**
  - Initiation, titration, and concomitant-medication adjustment
  - Continuous monitoring of blood potassium, sugar, and pressure

300 mg
Recommended starting dose

600 mg
Dose titration

900 mg
Dose titration

1200 mg
Maximum dose

85% of patients, who achieved a positive clinical response, achieved initial improvement at or above 600 mg/day[2]

DOSE UP IF TREATMENT GOALS ARE NOT MET AND PATIENT IS TOLERATING KORLYM

Decisions about dose increases should be based on clinical assessment of tolerability and the degree of improvement in Cushing's syndrome manifestations.

Because of the variability in clinical presentation and variability of response in the open-label trial, it is uncertain whether change in body weight or psychiatric symptoms could be ascribed to the effects of Korlym.[1]

IMPORTANT DOSING CONSIDERATIONS[1,2]:

- Renal impairment: Do not exceed 600 mg once daily
- Mild-to-moderate hepatic impairment: Do not exceed 600 mg once daily. Do not use in severe hepatic impairment
- 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
- Concomitant use of Korlym with a strong CYP3A inhibitor resulted in a 38% increase in mean plasma concentration of mifepristone. For patients already being treated with a strong CYP3A inhibitor, start with a Korlym dose of 300 mg/day and titrate to a maximum of 900 mg/day if clinically indicated
- When a strong CYP3A inhibitor is administered to patients already receiving Korlym, adjust the dose as follows: for patients receiving a daily dose of 600 mg, reduce the daily dose to 300 mg. For patients receiving a daily dose of 900 mg, reduce dose to 600 mg. For patients receiving a daily dose of 1200 mg, reduce dose to 900 mg. Titrate if clinically indicated and do not exceed a Korlym dose of 900 mg in combination with a strong CYP3A inhibitor
- Administer Korlym once daily orally with a meal. Patients should swallow the tablet whole and should not split, crush, or chew tablets
- Most common adverse events (fatigue, headache, nausea, and peripheral edema) did not increase with increasing dose
- Potassium supplementation or the use of mineralocorticoid-receptor antagonists may be employed to normalize potassium levels

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IMPROVING MEASURES THAT MATTER

60%
of patients (n=25) had a reduction in $AUC_{glucose}$ of ≥25% by Week 24/ET[3]*

1.1%
significant mean reduction in HbA1c by Week 24/ET[1†]

~2%
mean reduction in subset of patients with HbA1c >7% (n=12) at baseline was achieved by Week 24/ET[3,4†]

7 OF 15
patients taking Korlym had their antidiabetic medications reduced[3]

5 OF 12
patients had their insulin reduced by at least half[3]

5.7% (6.3 kg)
reduction in mean body weight at Week 24/ET (P<.001)[3]

Improvement in glucose from baseline seen as early as
6 weeks[4]

Reduction in waist circumference[3]
♀ **6.8 ± 5.8 CM** (P<.001)
♂ **8.4 ± 5.9 CM** (P<.001)

60%
of patients (n=25) had a meaningful positive change in mood by Week 24/ET[4†,‡]

Because of the variability in clinical presentation and variability of response in this open-label study, it is uncertain whether psychiatric and weight changes could be ascribed to the effects of Korlym.[1]

AUC=area under the curve; ET=early termination.

*Assessed by oral glucose tolerance test.

†Study design: SEISMIC (Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing's Syndrome) was a phase 3, uncontrolled, open-label, 24-week, multicenter clinical study of 50 subjects with endogenous Cushing's syndrome who failed surgery or were not candidates for surgery. All 50 subjects had clinically significant hypercortisolism. Subjects received 300 mg to 1200 mg of Korlym per day for up to 24 weeks. Forty-three patients had Cushing disease, of which 42 had previously undergone pituitary surgery. Four patients had ectopic adrenocorticotropic hormone secretion, and 3 had adrenal carcinoma. Forty-six subjects received at least 30 days of dosing during the 24-week study period and were included in a modified intent-to-treat analysis.[2,4]

‡These patients experienced an 11-point improvement in BDI-II (from a score of 23 [defined as moderate depression] to 12 [defined as minimal depression]).[4]

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DOSAGE AND ADMINISTRATION

Obtain a negative pregnancy test prior to initiating treatment with Korlym in females of reproductive potential, or if treatment is interrupted for more than 14 days.

Administer once daily orally with a meal. The recommended starting dose is 300 mg once daily. Renal impairment: Do not exceed 600 mg once daily. Mild-to-moderate hepatic impairment: Do not exceed 600 mg once daily. Do not use in severe hepatic impairment. 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.

Concomitant use of Korlym with a strong CYP3A inhibitor resulted in a 38% increase in mean plasma concentration of mifepristone. For patients already being treated with a strong CYP3A inhibitor, start with a Korlym dose of 300 mg per day and titrate to a maximum of 900 mg per day if clinically indicated.

When a strong CYP3A inhibitor is administered to patients already receiving Korlym, adjust the dose as follows: for patients receiving a daily dose of 600 mg, reduce dose to 300 mg. For patients receiving a daily dose of 900 mg, reduce dose to 600 mg. For patients receiving a daily dose of 1200 mg, reduce dose to 900 mg. Titrate if clinically indicated and do not exceed a Korlym dose of 900 mg in combination with a strong CYP3A inhibitor.

CONTRAINDICATIONS

Pregnancy; patients taking simvastatin or lovastatin and CYP3A substrates with narrow therapeutic ranges; patients receiving systemic corticosteroids for lifesaving purposes; women with a history of unexplained vaginal bleeding or endometrial hyperplasia with atypia or endometrial carcinoma; patients with known hypersensitivity to mifepristone or to any of the product components.

WARNINGS AND PRECAUTIONS

Adrenal insufficiency: Patients should be closely monitored for signs and symptoms of adrenal insufficiency.

Hypokalemia: Hypokalemia should be corrected prior to treatment and monitored for during treatment.

Vaginal bleeding and endometrial changes: Women may experience endometrial thickening or unexpected vaginal bleeding. Use with caution if the patient also has a hemorrhagic disorder or is on anticoagulant therapy.

QT interval prolongation: Avoid use with QT interval-prolonging drugs, or in patients with potassium channel variants resulting in a long QT interval.

Use of strong CYP3A inhibitors: Concomitant use increases mifepristone plasma levels. Adjust Korlym dose as described in Dosage and Administration. Use only when necessary and do not exceed a Korlym dose of 900 mg.

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.

DRUG INTERACTIONS

Drugs metabolized by CYP3A: Administer drugs that are metabolized by CYP3A at the lowest dose when used with Korlym.

CYP3A inhibitors: Caution should be used when Korlym is used with strong CYP3A inhibitors. Adjust Korlym dose as described in Dosage and Administration. Use only when necessary, and do not exceed a Korlym dose of 900 mg.

CYP3A inducers: Do not use Korlym with CYP3A inducers.

Drugs metabolized by CYP2C8/2C9: Use the lowest dose of CYP2C8/2C9 substrates when used with Korlym.

Drugs metabolized by CYP2B6: Use of Korlym should be done with caution with bupropion and efavirenz.

Hormonal contraceptives: Do not use with Korlym.

USE IN SPECIFIC POPULATIONS

Lactation: Mifepristone is present in human milk, however, there are no data on the amount of mifepristone in human milk, the effects on the breastfed infant, or the effects on milk production during long term use of mifepristone.

References: 1. Korlym [prescribing information]. Menlo Park, CA: Corcept Therapeutics, Inc; 2019. **2.** Yuen KCJ, et al. *Endocr Pract.* 2015;21(10):1087-1092. **3.** Fleseriu M, et al. *J Clin Endocrinol Metab.* 2012;97(6):2039-2049. **4.** Data on file. Corcept Therapeutics Incorporated. Menlo Park, CA.

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