PDL NEW DRUG REVIEW

Proprietary Name: Korlym®
Common Name: mifepristone
PDL Category: Diabetic - Other

Summary

Indications and Usage: 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. Korlym® should not be used in the treatment of those with type 2 diabetes unless it is secondary to Cushing's syndrome. This is a pregnancy category X medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug Interactions: Please refer to Contraindications section that lists drugs that are CYP3A substrates and contraindicated with Korlym® use.

CYP3A4 inhibitors, such as ketoconazole, itraconazole, nefazodone, and others, could increase mifepristone levels. Thus, dose reductions of Korlym® may be needed. This combination should be used with extreme caution and the dose of Korlym® should be limited to 300mg and only used if necessary. Moderate CYP3A4 inhibitors, such as ciprofloxacin and erythromycin, should be used with caution in combination with Korlym®.

While the combination of Korlym® with CYP3A inducers (such as rifampin, phenytoin, and carbamazepine) has not studied, it is recommended that the combination be avoided.

Korlym® is an inhibitor of CYP2C8/2C9 and can significantly increase levels of drugs that are substrates of CYP2C8/2C9 (such as fluvastatin, NSAIDS, warfarin). Thus, if these substrates of CYP2C are used concomitantly with Korlym®, the smallest recommended dose should be used and patients should be monitored closely.

While the combination of mifepristone and substrates of CYP2B6 have not been studied, concomitant use should be done with caution as mifepristone is an inhibitor of CYP2B6. Mifepristone may cause significant increases in levels of CYP2B6 substrates.

Mifepristone interferes with the effectiveness of hormonal contraceptives; therefore, non-hormonal methods of contraception should be used.

Dosage Forms: Tablets, 300mg

Recommended Dosage: Recommended starting dose is 300mg once daily. The dose may be increased to a maximum of 1200mg once daily, but should not exceed 20mg/kg/day. The maximum dose in those with renal impairment and in those with mild to moderate hepatic impairment is 600mg. Korlym® use is not recommended in those with severe hepatic impairment.

Common Adverse Drug Reactions: *There was no placebo data available.* The most commonly reported adverse events included nausea (48%), vomiting (26%), dry mouth (18%), diarrhea (12%),

constipation (10%), fatigue (48%), peripheral edema (26%), pain (14%), headache (44%), dizziness (22%), somnolence (10%), arthralgia (30%), back pain (16%), myalgia (14%), pain in extremity (12%), decreased blood potassium (34%), abnormal thyroid function test (18%), sinusitis (14%), nasopharyngitis (12%), decreased appetite (20%), anorexia (10%), hypertension (24%), endometrial hypertrophy (28%), dyspnea (16%), and anxiety (10%).

Use of Korlym® may also result in adrenal insufficiency, hypokalemia, vaginal bleeding and endometrial changes, QT interval prolongation, exacerbations/deterioration of conditions treated with corticosteroids, and *Pneumocystis jiroveci* infection.

Contraindications: In pregnant women; In those taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, due to the potential for increased risk of adverse events; In those who require concomitant treatment with systemic corticosteroids for serious medical conditions or illnesses (eg. immunosuppression after organ transplantation); In women with a history of unexplained vaginal bleeding; In women with endometrial hyperplasia with atypia or endometrial carcinoma; In those with a hypersensitivity to mifepristone or any component of the compound.

Manufacturer: Corcept Therapeutics Incorporated

Analysis: Mifepristone, the active ingredient of Korlym®, is a cortisol receptor blocker. It is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses, but with little affinity for the mineralocorticoid receptor (MR, GR-I). Keeping in mind the contraindications of use, pregnancy must be excluded before treatment is initiated or if treatment is interrupted for more than 14 days in women of reproductive potential. During Korlym® use and for one month after stopping treatment, non-hormonal contraceptives should be used in all women of reproductive potential.

One uncontrolled, open-label study (N=50) assessed the efficacy of Korlym® for treatment of endogenous Cushing's syndrome. The study included 2 cohorts: a diabetes cohort (N=29) and a hypertension cohort (N=21). In the hypertension cohort, there were no changes in mean systolic and diastolic blood pressure changes at the end of the study compared with baseline. In the diabetes cohort, the primary efficacy analysis was of responders, defined as a patient who had ≥25% reduction from baseline in glucose AUC. 60% (N=15/25) were treatment responders. Furthermore, 24 patients had obtainable HbA1c values at baseline and at the end of the study. The mean reduction of HbA1c for this group was 1.1%. Of the 15 subjects taking antidiabetic medications, 7 subjects had their meds reduced and with the others the medications remained constant.

It is recommended that Korlym® remain non-preferred and recommend the Drug Utilization Review (DUR) Commission develop criteria.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Korlym [package insert]. Menlo Park, CA: Corcept Therapeutics Incorporated; 2012.