CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202107Orig1s008

Trade Name:	KORLYM
Generic or Proper Name:	mifepristone
Sponsor:	Corcept Therapeutics, Inc.
Approval Date:	November 5, 2019
Indication:	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.

CENTER FOR DRUG EVALUATION AND RESEARCH

202107Orig1s008

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	**X**
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s008

APPROVAL LETTER

NDA 202107/S-008

SUPPLEMENT APPROVAL

Corcept Therapeutics
Attention: Susan Rinne
Vice President, Corporate Regulatory Affairs
149 Commonwealth Drive
Menlo Park, CA 94025

Dear Ms. Rinne:

Please refer to your supplemental new drug application (sNDA) dated and received March 30, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Korlym (mifepristone) tablets, 300 mg.

This Prior Approval supplemental new drug application provides for the revisions to the prescribing information (PI) to include the results from Study C1073-38 titled, *A Phase 1, Open-Label, Drug-drug Interaction Study in Healthy Subjects to Determine the Effects of a Strong Inhibitor (Itraconazole) of Cytochrome P450 3A on Exposure to Mifepristone and Its Metabolites*. Specific sections of the PI impacted by this information are:

1. Dosage and Administration section, 2.4 Concomitant Administration with CYP3A4 Inhibitors subsection,
2. Warnings and Precautions section, 5.6 Use of Strong CYP3A4 inhibitors subsection
3. Drug Interactions section, 7.2 CYP3A4 Inhibitors subsection
4. Clinical Pharmacology section, 12.3 Pharmacokinetics subsection

The supplement also provides for revisions to the PI to comply with the Pregnancy Lactation Labeling Rule (PLLR).

The Medication Guide (MG) has also been revised to be consistent with the PLLR revisions to the PI and other editorial revisions.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending "Changes Being

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at 301-796-2194.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
11/05/2019 03:05:54 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s008

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KORLYM® safely and effectively. See full prescribing information for KORLYM®.
KORLYM® (mifepristone) 300 mg Tablets
Initial U.S. Approval 2000

WARNING: TERMINATION OF PREGNANCY

See full prescribing information for complete boxed warning.

Mifepristone has potent antiprogestational effects and will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with KORLYM, or if treatment is interrupted for more than 14 days in females of reproductive potential.

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.5) 10/2019

----------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 (1).

- **Important Limitations of Use:** Do not use for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome.

----------DOSAGE AND ADMINISTRATION----------
- Obtain a negative pregnancy test in females of reproductive potential prior to initiating treatment with KORLYM or if treatment is interrupted for more than 14 days. (2.1)
- Administer once daily orally with a meal (2.2).
- The recommended starting dose is 300 mg once daily (2.2).
- 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 (2.2).
- Renal impairment: do not exceed 600 mg once daily (2.3).
- Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment (2.4).
- Concomitant administration with strong CYP3A inhibitors: Do not exceed 900 mg once daily (2.5).

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 300 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4, 8.1)
- Patients taking drugs metabolized by CYP3A such as simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges (4)
- Patients receiving systemic corticosteroids for lifesaving purposes (4)
- Women with a history of unexplained vaginal bleeding or endometrial hyperplasia with atypia or endometrial carcinoma (4)
- Patients with known hypersensitivity to mifepristone or to any of the product components (4)

----------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 can increase mifepristone plasma levels. Use only when necessary and limit mifepristone dose to 900 mg (5.6).

----------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 (6).

To report suspected adverse reactions, contact Corcept Therapeutics at 1-855-844-3270 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Drugs metabolized by CYP3A: Administer drugs that are metabolized by CYP3A at the lowest dose when used with KORLYM (7.1).
- CYP3A inhibitors: Caution should be used when KORLYM is used with strong CYP3A inhibitors. Limit mifepristone dose to 900 mg per day when used with strong CYP3A inhibitors (7.2).
- CYP3A inducers: Do not use KORLYM with CYP3A inducers (7.3).
- Drugs metabolized by CYP2C8/2C9: Use the lowest dose of CYP2C8/2C9 substrates when used with KORLYM (7.4).
- Drugs metabolized by CYP2B6: Use of KORLYM should be done with caution with bupropion and efavirenz (7.5).
- Hormonal contraceptives: Do not use with KORLYM (7.6).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING 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 non-hormonal 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.

1 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.

LIMITATIONS OF USE:

- KORLYM should not be used in the treatment of patients with type 2 diabetes unless it is secondary to Cushing’s syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to and During KORLYM Administration

Obtain a negative pregnancy test in females of reproductive potential prior to initiating treatment with KORLYM or if treatment is interrupted for more than 14 days *[see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.1, 8.3)]*.

2.2 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, striae, 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 reinitiated 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.

2.3 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)]*

2.4 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)]*

2.5 Concomitant Administration with CYP3A Inhibitors

Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole may increase exposure to mifepristone. KORLYM should be used in combination with strong CYP3A inhibitors only when necessary. *[See Warnings and Precautions (5.6), Drug Interactions (7.2)]*

Administration of KORLYM to patients already being treated with strong CYP3A inhibitors:

- Start at a dose of 300 mg. If clinically indicated, titrate to a maximum of 900 mg.

Administration of strong CYP3A inhibitors to patients already being treated with KORLYM:

- Adjust the dose of KORLYM according to Table 1.

Table 1. Dose adjustment of KORLYM when strong CYP3A inhibitor is added

Current dose of KORLYM	Adjustment to dose of KORLYM if adding a strong CYP3A inhibitor
300 mg	No change
600 mg	Reduce dose to 300 mg. If clinically indicated, titrate to a maximum of 600 mg
900 mg	Reduce dose to 600 mg. If clinically indicated, titrate to a maximum of 900 mg
1200 mg	Reduce dose to 900 mg

3 DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg

Oval shaped, light yellow to yellow tablets debossed with “Corcept” on one side and “300” on the other side. The tablets are not scored.

4 CONTRAINDICATIONS

KORLYM is contraindicated in:

- Pregnancy *[See Dosage and Administration (2.1), Use in Specific Populations (8.1,8.3)]*
- Patients taking drugs metabolized by CYP3A such as simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, 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)]*
- Patients receiving systemic corticosteroids for lifesaving purposes (e.g., immunosuppression after organ transplantation) because KORLYM antagonizes the effect of glucocorticoids.
- Women with a history of unexplained vaginal bleeding or with endometrial hyperplasia with atypia or endometrial carcinoma.
- Patients with known hypersensitivity 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 hypoadrenalism 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).

Treatment with KORLYM at a lower dose can be resumed after resolution of adrenal insufficiency. Patients should also be evaluated for precipitating causes of hypoadrenalism (infection, trauma, etc.).

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 dilatation 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 IKr. 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 caution in patients taking ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole, as these could increase the concentration of mifepristone in the blood. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. KORLYM should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to 900 mg per day. *[See Warnings & Precautions (5.4), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]*

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 Hypercortisolemia

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 hypertrophy. 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 2.

Table 2. Treatment Emergent Adverse Events Occurring in ≥10% of Cushing's Syndrome Patients Receiving KORLYM

Body System/Adverse Reaction	Percent (%) of Patients Reporting Event (n = 50)
Gastrointestinal disorders	
Nausea	48
Vomiting	26
Dry mouth	18
Diarrhea	12
Constipation	10
General disorders and administration/site conditions	
Fatigue	48
Edema peripheral	26
Pain	14
Nervous system disorders	
Headache	44
Dizziness	22
Somnolence	10
Musculoskeletal and connective tissue disorders	
Arthralgia	30
Back pain	16
Myalgia	14
Pain in extremity	12
Investigations	
Blood potassium decreased	34
Thyroid function test abnormal	18
Infections and infestations	
Sinusitis	14
Nasopharyngitis	12
Metabolism and nutrition disorders	
Decreased appetite	20
Anorexia	10
Vascular disorders	
Hypertension	24
Reproductive system and breast disorders	
Endometrial hypertrophy	38*
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	16
Psychiatric disorders	
Anxiety	10

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

Laboratory Tests

Reductions in high density lipoprotein-cholesterol (HDL-C) levels have been observed following treatment with KORLYM. In study subjects that experienced declines in HDL-C, levels returned to baseline following discontinuation of drug. The clinical significance of the treatment-related reduction in HDL-C 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 or eplerenone). 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.

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.

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: gastroesophageal 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: muscular weakness, flank pain, musculoskeletal chest pain

Psychiatric disorders: insomnia

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia *[See Warnings and Precautions (5.3)]*

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.

Rash

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

6.2 Postmarketing Experience

The following adverse reaction has been identified during post approval use of KORLYM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Angioedema

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, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, 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, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir /ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole may increase exposure to mifepristone. Caution should be used when strong CYP3A inhibitors are prescribed 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 900 mg, and strong inhibitors of CYP3A should be used only when necessary. *[See Dosage and Administration (2.4), Warnings & Precautions (5.6), and Clinical Pharmacology (12.3)]*

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, rifapentin, 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 fluvastatin, a typical CYP2C8/2C9 substrate, in healthy subjects. When given concomitantly with KORLYM, drugs that are substrates of CYP2C8/2C9 (including non-steroidal anti-inflammatory drugs, warfarin, and repaglinide) 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 study has 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. *[See Use In Specific Populations (8.3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

KORLYM is contraindicated in pregnancy because the use of KORLYM results in pregnancy loss. There are no data that assess the risk of birth defects in women exposed to KORLYM during pregnancy. Available data limited to exposure following a single dose of mifepristone during pregnancy showed a higher rate of major birth defects compared to the general population comparator *(See Data)*. Mifepristone administered to pregnant mice, rats, and rabbits during organogenesis caused pregnancy loss in all species at clinically relevant doses based on body surface area comparisons *(See Data)*.The inhibition of both endogenous and exogenous progesterone by mifepristone at the progesterone 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)]*

The estimated risk of fetal loss is elevated in patients with active Cushing's syndrome (24-30%), and the risk of major birth defects is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Human Data

There are no data on long term exposure to mifepristone in pregnancy. Available data are limited to exposure to a single dose of mifepristone for pregnancy termination. In a prospective study in France of 46 pregnancies exposed to a single dose of mifepristone alone and 59 pregnancies exposed to a single dose of mifepristone and misopristol, the overall major birth defect rate (4%) was greater than the general population background rate of 2 to 3% (2 birth defects in each group). There was no pattern of birth defects identified.

Animal Data

Reproductive studies were performed 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). 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 mifepristone did not cause any adverse developmental effects in rats or mice during organogenesis. These deformities were most likely due to the mechanical effects of uterine contractions resulting from antagonism of the progesterone receptor.

8.2 Lactation

Risk Summary

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 *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Korlym and any potential adverse effects on the breastfed child from Korlym or from the underlying maternal condition.

Clinical Considerations

To minimize exposure to a breastfed infant, women who discontinue or interrupt KORLYM treatment may consider pumping and discarding milk during treatment and for 18-21 days (5-6 half-lives) after the last dose, before breastfeeding.

Data

Available published data based on intake of a single dose of 600 mg of mifepristone in 10 breastfeeding women who were 6-12 months postpartum showed a small amount in breast milk (the estimated relative infant dose was 0.5%). The half-life of mifepristone is longer with repeat dosing compared to a single dose; therefore, there may be greater exposure with long term use.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Due to its anti-progestational activity, KORLYM causes pregnancy loss. Perform pregnancy testing before the initiation of treatment with KORLYM or if treatment is interrupted for more than 14 days in females of reproductive potential.

Contraception

Recommend non-hormonal contraception for the duration of treatment and for one month after stopping treatment . KORLYM interferes with the effectiveness of hormonal contraceptives. *[See Drug Interactions (7.6)]*

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

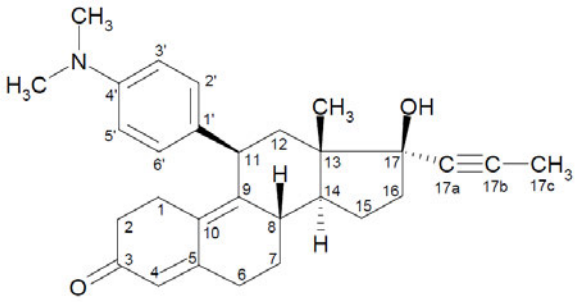
In patients with mild to moderate hepatic impairment, the maximum dose should not exceed 600 mg per day. The pharmacokinetics of mifepristone in patients with severe hepatic impairment has not been studied, and KORLYM should not be used in these patients. *[See Clinical Pharmacology (12.3)]*

10 OVERDOSAGE

There is no experience with overdosage of KORLYM.

11 DESCRIPTION

KORLYM (mifepristone) is a cortisol receptor blocker for oral administration. The chemical name of mifepristone is 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4, 9-dien-3-one. The chemical formula is $C_{29}H_{35}NO_2$; the molecular weight is 429.60, and the structural formula is:



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, polysorbate 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% (mifepristone), 61% (metabolite 1), 48% (metabolite 2), and 45% (metabolite 3)] than either dexamethasone (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

Cytochrome 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: 0.95 [0.52-1.71]; 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, CYP2C8/2C9, 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 3)

Table 3. Summary Table of KORLYM Drug-Drug Interaction Effects

Dosing of Mifepristone	Coadministered Drug	Dosing of Coadministered Drug	Geometric Mean Ratio (analyte ratio with/without drug coadministration)		
			Analyte	AUC	Cmax
Effect of KORLYM on Coadministered Drug					
Contraindicated with mifepristone *[See Contraindications (4)]*					
1200 mg once daily for 10 days	simvastatin[1]	80 mg single dose	simvastatin acid simvastatin	15.70 10.40	18.20 7.02
Use lowest dose of coadministered drug, based on clinical experience and/or use of therapeutic drug monitoring					
1200 mg once daily for 10 days	alprazolam[2]	1 mg single dose	alprazolam 4-hydroxy-alprazolam	1.80 0.76	0.81 0.39
1200 mg once daily for 7 days	fluvastatin[3]	40 mg single dose	fluvastatin	3.57	1.76
1200 mg once daily for 10 days	digoxin[4]	0.125 mg once daily	digoxin	1.40	1.64
Effect of Coadministered Drug on KORLYM					
Dose adjustment required					
600 mg once daily for 17 days	ketoconazole	200 mg bid on days 13-17	mifepristone Metabolite 1†	1.38 1.02	1.28 1.06

			Metabolite 2†	1.67	1.69
			Metabolite 3†	0.95	0.96
900 mg once daily for 14 days	itraconazole	200 mg daily for 14 days	mifepristone	1.10	1.20
			Metabolite 1†	1.04	1.00
			Metabolite 2†	1.23	1.19
			Metabolite 3†	0.97	0.94
Effect of Coadministered Drug on KORLYM					
No dosing adjustment required					
300 mg once daily for 14 days	cimetidine[5]	800 mg once daily	mifepristone	0.85*	0.75

*No effect = 90% CI within range 0.80 – 1.25
†See Section 12.2 for the relative potencies of the three metabolites

[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, pimozide, 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 CYP2C8/C9 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 mild inhibitors of CYP3A

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). However, following withdrawal of treatment and subsequent resumption of the estrus cycle, there was no effect on reproductive function when mated.

A single subcutaneous dose of mifepristone (up to 100 mg/kg) to rats on the first day after birth did not adversely affect future reproductive function in males or females, although the onset of puberty was slightly premature in dosed females. Repeated doses of mifepristone (1 mg every other day) to neonatal rats resulted in potentially adverse fertility effects, including oviduct 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 hypercortisolemia despite prior surgical treatment and radiotherapy. The reasons for medical treatment were failed surgery, recurrence of disease, and poor medical candidate for surgery. Forty-three patients (86%) had Cushing's disease, four patients (8%) had ectopic ACTH secretion, and three (6%) had adrenal carcinoma. Baseline characteristics included: mean age of 45 years (range 26 to 71), mean BMI of 36 kg/m^2 (range 24 to 66), mean weight 100 kg (range 61 to 199), and mean waist circumference was 119 cm (range 89 to 178); 70% were female; 84% were white and 16% were black or African American. Baseline mean urinary free cortisol level was 365 µg per 24 hr.

Patients belonged to one of two cohorts: a "diabetes" cohort (29 patients, 26 with type 2 diabetes and 3 with glucose intolerance), and a "hypertension" cohort (21 patients). Efficacy was evaluated separately in the two cohorts. KORLYM treatment was started in all patients at a dose of 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) defined 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. Fourteen 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 "Corcept" 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 every patient.

17.1 Importance of Preventing Pregnancy

- Advise patients that KORLYM will cause termination of pregnancy. KORLYM is contraindicated in pregnant patients.
- KORLYM reduces the effectiveness of hormonal contraceptives. 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.

Medication Guide
KORLYM® (KOR-Lim)
(mifepristone)
tablets

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.

Do not take KORLYM if you:

- **are pregnant.** See "What is the most important information I should know about KORLYM?"
- **are taking:**
  - simvastatin (Zocor®, Vytorin®, Simcor®)
  - lovastatin (Mevacor®, Altoprev®, Advicor®)
  - cyclosporine (Gengraf®, Neoral®, Restasis®, Sandimmune®)
  - dihydroergotamine (Migranal®)
  - ergotamine (Ergomar®, Migergot®)
  - fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Sublimaze Preservative Free®, Subsys®)
  - pimozide (Orap®)
  - quinidine (Nuedexta®)
  - sirolimus (Rapamune®, Torisel®)
  - tacrolimus (Prograf®, Protopic®)
- must take corticosteroid medicines for other serious medical problems
- are 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:

- are pregnant or plan to become pregnant
- 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.

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
  - high blood pressure
- 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.

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?"**
- **loss of pregnancy**
- **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 (hypoglycemia)
- **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.
- **disruption of menstrual cycle**
- **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
- pain in your arms and legs (arthralgia)
- swelling of your arms and legs (peripheral edema)
- dizziness
- low potassium in your blood
- vomiting
- high blood pressure
- 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.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KORLYM?
Store KORLYM at room temperature, between 68°F to 77°F (20°C to 25°C).
Keep KORLYM and all medicines out of the reach of children.

General information about the safe and effective use of KORLYM
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
Do not use KORLYM for a condition for which it was not prescribed. Do not give KORLYM to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about KORLYM that is written for healthcare professionals.

What are the ingredients in KORLYM?
Active ingredient: mifepristone
Inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.
Manufactured for: Corcept Therapeutics Incorporated, Menlo Park, CA 94025
KORLYM® is a registered trademark of Corcept Therapeutics Incorporated.

K-00004 XX XXXX
For more information, go to www.korlym.com or www.corcept.com or call 1-855-456-7596.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 11/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s008

NON-CLINICAL REVIEW(S)

Memorandum

PHARMACOLOGY/TOXICOLOGY MEMO TO FILE

Date	14 January 2019
NDA	202107 (SDN 284)
Sponsor	Corcept
Drug	Korlym® (mifepristone) 300
Drug Class	Cortisol receptor blocker
Reviewer	Patricia Brundage
RE	PLLR Labeling Changes

The sponsor submitted a Prior Approval Labeling Supplement containing their proposal for revisions to the Package Insert (Pl) and Medication Guide from the results of Study C1073-38 titled, "A Phase 1, Open-Label, Drug-drug Interaction Study in Healthy Subjects to Determine the Effects of a Strong Inhibitor (ltraconazole) of Cytochrome P450 3A on Exposure to Mifepristone and Its Metabolites." The supplement also included label changes in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). Below are the Division's proposed nonclinical PLLR labeling changes (in red) in Section 8.1.

Proposed Nonclinical PLLR Labeling Changes

8.1 Pregnancy

Risk Summary

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. There are no well-controlled studies describing the risk of harm to infants born to women exposed to KORLYM during pregnancy *[See Data]*. Mifepristone administered to pregnant mice, rats, and rabbits during organogenesis caused (b) (4) (b) (4)-pregnancy loss (b) (4) in (b) (4) all species (b) (4) at clinically relevant (b) (4) doses based on body surface area comparisons *[See Data]*. The inhibition of both endogenous and exogenous progesterone by mifepristone at the progesterone 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.* (b) (4)

The estimated risk of fetal loss is elevated in patients with active Cushing's syndrome (24-30%), and the risk of major birth defects is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Human Data

(b) (4) . In a prospective study of 46 pregnancies exposed to mifepristone alone and 59 pregnancies exposed to mifepristone and misopristol, the overall (b) (4)

Animal Data

(b) (4) Reproductive studies were performed 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) (b) (4) 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 mifepristone did not cause any (b) (4) adverse developmental effects (b) (4) (b) (4) in rats or mice during organogenesis. These deformities were most likely due to the mechanical effects of uterine contractions resulting from antagonism of the progesterone receptor.

8.2 Lactation

Risk Summary

Mifepristone is present in human milk (b) (4) *[See Data]*. No information on the effects of Korlym in breastfed infants is available.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Korlym and any potential adverse effects on the breastfed child from Korlym or from the underlying maternal condition.

Data

(b) (4)

(b) (4)

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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.

Contraception

(b) (4)

KORLYM will interfere with the effectiveness of hormonal contraceptives. *[See Drug Interactions (7.6)]* Recommend contraception for the duration of treatment and for one month after stopping treatment (b) (4)

(b) (4)

(b) (4)

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)]*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICIA M BRUNDAGE
07/16/2019 04:01:26 PM

TODD M BOURCIER
07/17/2019 07:39:58 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s008

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA Number	202107
Link to EDR	\\CDSESUB1\evsprod\NDA202107\202107.enx
Submission Date	03/30/2018
Submission Type	Labeling supplement
Brand Name	Korlym
Generic Name	Mifepristone
Dosage Form and Strength	Tablets, 300 mg
Route of Administration	Oral administration,
Proposed Indication	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
Applicant	Corcept Therapeutics
Associated IND	IND 076480
OCP Review Team	*Jianmeng Chen, M.D., Ph.D* ; *Jayabharathi Vaidyanathan, PhD*

APPEARS THIS WAY ON ORIGINAL

1. Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in study C-1073-38, and agrees with the proposed dose adjustment for korlym when used in combination with strong CYP3A inhibitors.

KORLYM should be used in combination with strong CYP3A inhibitors only when necessary and the dose should be limited to 900 mg per day. The proposed language in Highlights, Section 2.4, Section 5.6, Section 7.2 and Section 12.3 of the label is acceptable. Refer to Table 3 for details.

.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Background

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. KORLYM was approved in the United States on Oct 23, 2014.

Mifepristone is a substrate of CYP3A4 and its three major active metabolites are products of CYP3A4-mediated metabolism. Mifepristone is also an inhibitor of CYP3A4. The effect of a strong CYP3A4 inhibitor such as ketoconazole on the pharmacokinetics of mifepristone was not evaluated at the time of NDA approval. The sponsor had proposed (b) (4). This proposal was not acceptable to the Agency (b) (4) could lead to safety concerns. This concern led to a post-marketing requirement for the sponsor to conduct a drug-drug interaction study between mifepristone and ketoconazole.

PMR 1875-2, Study C-1073-36 was conducted in healthy male volunteers to assess the effect of ketoconazole on mifepristone. The study was submitted on Apr 28, 2016 to fulfil PMR, and was reviewed by Dr. Suryanarayana Sista (DARRT date 11/28/2016). The administration of 600 mg Korlym once daily with 200 mg ketoconazole twice daily resulted in a 28% increase in mifepristone Cmax and a 38% increase in AUC0-24. The PMR study report submission did not include labeling changes.

Subsequently, the sponsor submitted a labeling supplement S007, proposed to change the dose recommendation for korlym coadministered with strong CYP3A inhibitors. The sponsor cited the PK result in Study C-1073-36 and proposed to limit the dose of KORLYM to 900 mg daily. The sponsor reasoned that with the corresponding increases

in Cmax and AUC0-24h (27.59% and 38.01%, respectively) when coadministered with strong CYP3A inhibitors, 900 mg KORLYM should yield systemic exposures similar in magnitude to those previously attained with 1200 mg daily (i.e., approximately the equivalent of 900•1.38=1242). However, the agency noted that mifepristone exhibits mechanism-based inhibition of its own metabolism, and the dose proportionality is questionable from 900 to 1200 mg. In the final label, korlym dose is restricted to 600 mg per day when used in combination with strong CYP3A inhibitors, as studied in Study C-1073-36.

In the current submission, this supplement includes Study C1073-38 titled, "A Phase 1, Open-Label, Drug-drug Interaction Study in Healthy Subjects to Determine the Effects of a Strong Inhibitor (ltraconazole) of Cytochrome P450 3A on Exposure to Mifepristone and Its Metabolites." The submission also includes proposed changes to the KORLYM prescribing information as follows:

- Proposed changes based on the results of Study Cl073-38
- Label changes in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

This review focused on the PK of mifepristone when used in combination with strong CYP3A inhibitors, and the recommendations based on the DDI study with itraconazole.

PK of mifepristone when used in combination with strong CYP3A inhibitors

Study C1073-38 demonstrated that administration of mifepristone 900 mg QD × 14 days with a strong CYP3A4 inhibitor, itraconazole 200 mg QD × 14 days, resulted in 10% [AUC(0-24)] to 20% (Cmax) increases in mifepristone exposure (Table 1). There were no significant changes in exposure to Metabolites RU-42633 and RU-42848 and slight (~ 23%) increases in exposure to Metabolite RU-42698 (Table 1).

A prior study, C1073-36, in which ketoconazole was used as the CYP3A4 inhibitor, demonstrated an increase in exposure to mifepristone and 2 of the 3 metabolites after a dose of 600 mg QD × 12 days alone and then concurrent with ketoconazole 200 mg BID × 5 days. The co-administration resulted in a 28% increase in mifepristone Cmax and a 38% increase in AUC_{0-24} (Table 1).

Table 1. Summary Table of KORLYM Drug-Drug Interaction (b) (4)

Dosing of Mifepristone	Coadministered Drug	Dosing of Coadministered Drug	Geometric Mean Ratio (analyte ratio with/without drug coadministration)		
			Analyte	AUC	Cmax
600 mg once daily for 17 days	ketoconazole	200 mg bid on days 13-17	mifepristone	1.38	1.28
			Metabolite 1†	1.02	1.06
			Metabolite 2†	1.67	1.69
			Metabolite 3†	0.95	0.96
900 mg once daily for 14 days	itraconazole	200 mg daily for 14 days	mifepristone	1.10	1.20
			Metabolite 1†	1.04	1.00
			Metabolite 2†	1.23	1.19
			Metabolite 3†	0.97	0.94

(Source: Table 3, proposed label)

Recommendations for mifepristone when used in combination with strong CYP3A inhibitors

Based on the Study C1073-36 and Study C1073-38, the coadministration with strong CYP3A inhibitors leads to 10-38% increase in mifepristone exposure (AUC). Therefore, the dose of KORLYM when administered with strong inhibitors of CYP3A4 should be limited to 900 mg; and strong inhibitors of CYP3A should be used only when necessary.

Based on Study C1073-36, 900 mg KORLYM should yield systemic exposures similar in magnitude to those previously attained with 1200 mg daily (i.e., approximately the equivalent of 900•1.38=1242). In Study C1073-38, the exposure of mifepristone and the 3 metabolites after administration of mifepristone 900 mg QD + itraconazole was comparable to that from mifepristone 1,200 mg QD, the maximum labeled dose (Table 2), supporting the proposed labeling change.

The labeling changes are summarized in Table 3. In section 2.4, we recommend the edits to reflect the revised recommendation, that when administered with strong CYP3A4 inhibitors, KORLYM should be limited to 900 mg.

Table 2. Estimates of the impact of inhibition of CYP3A4 on exposure to mifepristone and three metabolites — mifepristone 900 mg QD × 14 days + itraconazole 200 mg × 14 days vs. mifepristone 1,200 mg QD × 14 days alone

Analyte	Parameter	Geometric Mean Ratio (%)	90% CI
Mifepristone	Cmax	97.69	87.43 – 109.16
	AUC(0-24)	96.62	89.33 – 104.52
RU-42633	Cmax	90.95	84.56 – 97.83
	AUC(0-24)	91.58	85.48 – 98.12
RU-42698	Cmax	105.16	96.49 – 114.61
	AUC(0-24)	110.14	103.31 – 117.42
RU-42848	Cmax	86.00	79.61 – 92.91
	AUC(0-24)	89.82	84.26 – 95.74

(Source: Table 2, cover letter attachment)

Table 3. Proposed labeling changes based on Study C1073-38

<table>
<tr><td>Section</td><td colspan="2"></td></tr>
<tr><td rowspan="2">Highlight</td><td>Proposed Labeling Change</td><td>----------DOSAGE AND ADMINISTRATION----------
• Concomitant administration with strong CYP3A inhibitors: Do not exceed 900~~600~~ mg once daily (2.4).
-----WARNINGS AND PRECAUTIONS-----
• Use of Strong CYP3A Inhibitors: Concomitant use can increase mifepristone plasma levels. Use only when necessary and limit mifepristone dose to 900~~600~~ mg (5.6).
----------DRUG INTERACTIONS----------
• CYP3A inhibitors: Caution should be used when KORLYM is used with strong CYP3A inhibitors. Limit mifepristone dose to 900~~600~~ mg per day when used with strong CYP3A inhibitors (7.2).</td></tr>
<tr><td>FDA Recommendation</td><td>Acceptable</td></tr>
<tr><td>Section 2.4</td><td>Proposed Labeling Change</td><td>2.4 Concomitant Administration with CYP3A Inhibitors
Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole may increase exposure to mifepristone. KORLYM should be used in combination with strong CYP3A inhibitors only when necessary. [See Warnings and Precautions (5.6), Drug Interactions (7.2)]

Administration of KORLYM to patients already being treated with strong CYP3A inhibitors:
• Start at a dose of 300 mg. If clinically indicated, titrate to a maximum of 900~~600~~ mg.

Administration of strong CYP3A inhibitors to patients already being treated with KORLYM:
• Adjust the dose of KORLYM according to Table 1.

Table 1. Dose adjustment of KORLYM when strong CYP3A inhibitor is added
<table><tr><th>Current dose of KORLYM</th><th>Adjustment to dose of KORLYM if adding a strong CYP3A inhibitor</th></tr><tr><td>300 mg</td><td>No change</td></tr><tr><td>600 mg</td><td>Reduce dose to 300 mg. If clinically indicated, titrate to a maximum of 600 mg</td></tr><tr><td>900 mg</td><td>Reduce dose to 600 mg</td></tr><tr><td>1200 mg</td><td>Reduce dose to 900~~600~~ mg</td></tr></table></td></tr>
<tr><td></td><td>FDA Recommendation</td><td>Administration of strong CYP3A inhibitors to patients already being treated with KORLYM:
• Adjust the dose of KORLYM according to Table 1.

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</table>

<table>
<tr><td rowspan="2">Section 5.6</td><td>Proposed Labeling Change</td><td>KORLYM should be used with caution in patients taking ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole, as these could increase the concentration of mifepristone in the blood. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. KORLYM should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to 900~~600~~ mg per day. [See Warnings & Precautions (5.4), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]</td></tr>
<tr><td>FDA Recommendation</td><td>Acceptable</td></tr>
<tr><td rowspan="2">Section 7.2</td><td>Proposed Labeling Change</td><td>7.2 CYP3A Inhibitors
Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction o KORLYM may be required.

Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir /ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole may increase exposure to mifepristone. Caution should be used when strong CYP3A inhibitors are prescribed 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 900~~600~~ mg, and strong inhibitors of CYP3A should be used only when necessary. [See Dosage and Administration (2.4), Warnings & Precautions (5.6), and Clinical Pharmacology (12.3)]</td></tr>
<tr><td>FDA Recommendation</td><td>Acceptable</td></tr>
<tr><td rowspan="2">Section 12.3</td><td>Proposed Labeling Change</td><td>Table 3. Summary Table of KORLYM Drug-Drug Interaction Effects
<table>
<tr><th>Dosing of Mifepristone</th><th>Coadministered Drug</th><th>Dosing of Coadministered Drug</th><th colspan="3">Geometric Mean Ratio (analyte ratio with/without drug coadministration)</th></tr>
<tr><th></th><th></th><th></th><th>Analyte</th><th>AUC</th><th>Cmax</th></tr>
<tr><td rowspan="4">600 mg once daily for 17 days</td><td rowspan="4">ketoconazole</td><td rowspan="4">200 mg bid on days 13-17</td><td>mifepristone</td><td>1.38</td><td>1.28</td></tr>
<tr><td>Metabolite 1†</td><td>1.02</td><td>1.06</td></tr>
<tr><td>Metabolite 2†</td><td>1.67</td><td>1.69</td></tr>
<tr><td>Metabolite 3†</td><td>0.95</td><td>0.96</td></tr>
<tr><td rowspan="4">900 mg once daily for 14 days</td><td rowspan="4">itraconazole</td><td rowspan="4">200 mg daily for 14 days</td><td>mifepristone</td><td>1.10</td><td>1.20</td></tr>
<tr><td>Metabolite 1†</td><td>1.04</td><td>1.00</td></tr>
<tr><td>Metabolite 2†</td><td>1.23</td><td>1.19</td></tr>
<tr><td>Metabolite 3†</td><td>0.97</td><td>0.94</td></tr>
</table></td></tr>
<tr><td>FDA Recommendation</td><td>Acceptable</td></tr>
</table>

2. Individual study review

2.1. DDI study with itraconazole

Title: A Phase 1, Open-Label, Drug-drug Interaction Study in Healthy Subjects to Determine the Effects of a Strong Inhibitor (Itraconazole) of Cytochrome P450 3A on Exposure to Mifepristone and Its Metabolites

Objective: To the effect of treatment with a strong inhibitor of cytochrome P450 3A (CYP3A) enzymes (itraconazole 200 mg once daily [QD]) on the pharmacokinetic (PK) profile of mifepristone 900 mg QD and its active metabolites (mono-demethylated metabolite, RU 42633; hydroxylated metabolite, RU 42698; and di-demethylated metabolite, RU 42848) at steady-state when both drugs are administered with food.

Study design: Phase 1, single-center, open-label, fixed-sequence, drug-drug interaction study of the effect of multiple daily doses of oral itraconazole 200 mg, a strong inhibitor of CYP enzymes, given with mifepristone 900 mg QD, in healthy male subjects, where all drug administrations were given after a meal.

Eligible subjects participated in 3 study periods (days were numbered consecutively throughout the study); treatment regimens and durations were as follows:

- **Period 1, Days 1–14: mifepristone 1200 mg QD**
- **Period 2, Days 15–28: mifepristone 900 mg QD**
- **Period 3, Days 29–42: mifepristone 900 mg QD plus itraconazole 200 mg QD**

PK Sampling Schedule

Pharmacokinetic samples were collected at steady state for Periods 1, 2, and 3 (on the 14th day of the assigned treatment for the period) and on Day 43 during the follow-up period (Table 4).

Table 4. Pharmacokinetic Sampling Schedule: Mifepristone and Metabolites

Period 1 (Days 1 to 14)		Period 2 (Days 15 to 28)		Period 3 (Days 29 to 42)	
Days 1–13	**Day 14 PK Profile**	**Days 15–27**	**Day 28 PK Profile**	**Days 29–41**	**Day 42 PK Profile**
30 min predose [a]	30 min predose [a]	30 min predose [a]	30 min predose [a]	30 min predose [a]	30 min predose [a]
D1, 2, 4, 6, 8, 11, 12, 13	0.5 h	D15, 16, 18, 20, 22, 25, 26, 27	0.5 h	D29, 30, 32, 34, 36, 39, 40, 41	0.5 h
	1 h		1 h		1 h
	2 h		2 h		2 h
	3 h		3 h		3 h
	4 h		4 h		4 h
	5 h		5 h		5 h
	8 h		8 h		8 h
	12 h		12 h		12 h
	16 h		16 h		16 h
	24 h [b]		24 h [c]		24 h [d]

Note: see Table 9-7 for PK sampling windows.
D = study day.
[a] Single PK draw 30 minutes before dose of mifepristone in Periods 1-2 on the noted days and before dose of itraconazole in Period 3 on the noted days.
[b] 24-h sample on Day 14 was also the predose sample on Day 15.
[c] 24-h sample on Day 28 was also the predose sample on Day 29.
[d] 24-h sample on Day 42 was also the sample on Day 43.

(Source –Table 9-5, Study C1073-38 report)

Results:

Pharmacokinetic results

Administration of mifepristone 900 mg QD with a strong CYP3A4 inhibitor, itraconazole 200 mg QD, resulted in 9.7% (AUC) to 20.1% (Cmax) increase in mifepristone exposure, consistent with the inhibition of CYP3A4-mediated metabolism by itraconazole. As demonstrated in Figure 1, the exposure of mifepristone + itraconazole was comparable to that from mifepristone 1200 mg QD, the maximum labeled dose.

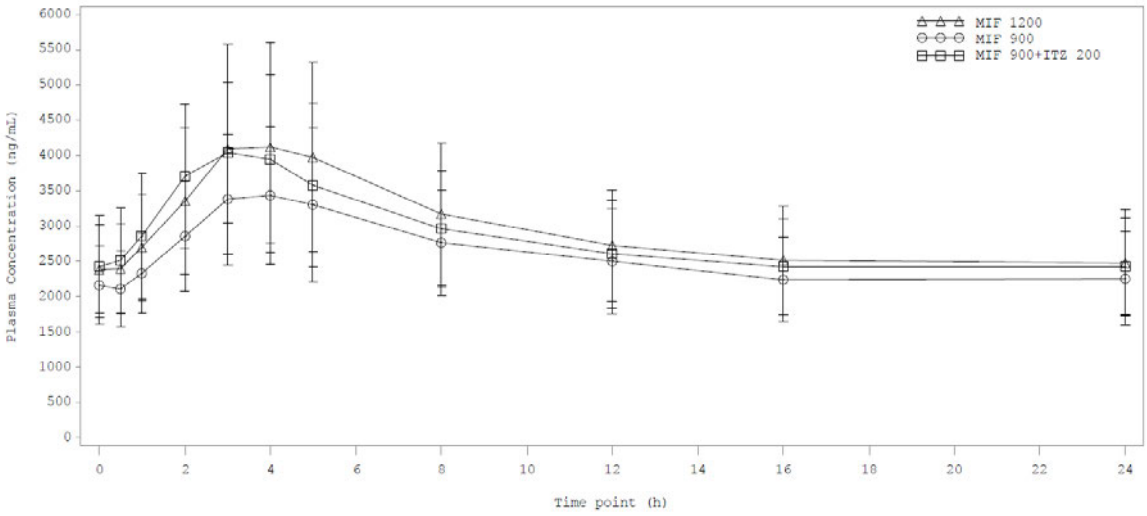

Figure 1. Mifepristone Plasma Pharmacokinetic Concentrations (ng/mL) at steady state (on the 14th day of assigned treatment for each period) when administered 1200 mg QD(MIT 1200), or 900 mg QD(MIT 900), or administered mifepristone 900 mg QD with concomitant itraconazole 200 mg QD (MIT 900+ITZ 200)

(Source: Figure 11-2, CSR C1073-38)

Summary statistics of PK parameters are presented in Table 5. In the comparison of mifepristone 900 mg + itraconazole to mifepristone 1200 mg alone, the GMRs for Cmax and AUC(0-24) were 97.69% (87.43, 109.16) and 96.62% (89.33, 104.52), respectively (Table 5). Mifepristone has three active metabolites, mono-demethylated (RU 42633), hydroxylated (RU 42698), and di-demethylated (RU 42848). Results with the 3 metabolites were concordant with those of the parent. This indicates that administration of mifepristone 900 mg QD in the presence of a strong CYP3A4 inhibitor results in exposure to mifepristone comparable to that from 1200 mg QD, the maximum labeled dose.

Table 5. Statistical Analysis of Pharmacokinetic Parameters of Mifepristone and Its Metabolites – Assessment of Pairwise Treatment Comparisons

Parameter Test/Reference	Adjusted Geometric Mean Test N=22	Adjusted Geometric Mean Reference N=22	GMR % (T/R)	90% CI of Ratio	CVw %
Mifepristone					
C_{max} (ng/mL)					
MIF+ITZ / MIF 1200	4260	4360	97.69	(87.43, 109.16)	22.15
MIF+ITZ / MIF 900	4260	3550	120.17	(107.55, 134.28)	
$AUC_{(0-24)}$ (ng.h/mL)					
MIF+ITZ / MIF 1200	65400	67700	96.62	(89.33, 104.52)	15.58
MIF+ITZ / MIF 900	65400	59600	109.72	(101.43, 118.68)	
Metabolite RU-42633					
C_{max} (ng/mL)					
MIF+ITZ / MIF 1200	1970	2160	90.95	(84.56, 97.83)	14.45
MIF+ITZ / MIF 900	1970	1970	99.89	(92.87,107.45)	
$AUC_{(0-24)}$ (ng.h/mL)					
MIF+ITZ / MIF 1200	41900	45800	91.58	(85.48, 98.12)	13.66
MIF+ITZ / MIF 900	41900	40300	104.00	(97.07,111.43)	
Metabolite RU-42698					
C_{max} (ng/mL)					
MIF+ITZ / MIF 1200	897	853	105.16	(96.49,114.61)	17.09
MIF+ITZ / MIF 900	897	755	118.83	(109.03,129.51)	
$AUC_{(0-24)}$ (ng.h/mL)					
MIF+ITZ / MIF 1200	18600	16900	110.14	(103.31,117.42)	12.68
MIF+ITZ / MIF 900	18600	15100	123.09	(115.46,131.24)	
Metabolite RU-42848					
C_{max} (ng/mL)					
MIF+ITZ / MIF 1200	1520	1770	86.00	(79.61, 92.91)	15.31
MIF+ITZ / MIF 900	1520	1630	93.61	(86.66, 101.13)	
$AUC_{(0-24)}$ (ng.h/mL)					
MIF+ITZ / MIF 1200	32800	36500	89.82	(84.26, 95.74)	12.64
MIF+ITZ / MIF 900	32800	33900	96.68	(90.70, 103.06)	

(Source –Table 11-1, Study C1073-38 report)

Conclusions:

• Administration of mifepristone 900 mg QD with a strong CYP3A4 inhibitor, itraconazole 200 mg QD, resulted in 9.7% (AUC) to 20.1% (Cmax) increase in mifepristone exposure. The exposure of 900 mg mifepristone + itraconazole was comparable to that from mifepristone 1200 mg QD, the maximum labeled dose.

• The results with the 3 metabolites were reasonably concordant with those of the parent.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JIANMENG CHEN
09/20/2018

JAYABHARATHI VAIDYANATHAN
09/20/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s008

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 202107/S008

Name of Drug: Korlym (mifepristone) tablets, 300 mg

Applicant: Corcept Therapeutics, Inc.

Labeling Reviewed

Submission Date: March 30, 2018, Prescribing Information (PI), MedGuide (MG)

Background and Summary Description:
Korlym was approved February 17, 2012, and is currently approved for the following indication:

> 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.

Supplement -008 was submitted to:

1. provide the results from Study C1073-38 titled *A Phase 1, Open-Label, Drug-drug Interaction Study in Healthy Subjects to Determine the Effects of a Strong Inhibitor (Itraconazole) of Cytochrome P450 3a on Exposure to Mifepristone and its Metabolites.*

   This information impacts the following sections of the PI: DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, and CINICAL PHARMACOLOGY, and

2. revise the PI to conform to the Pregnancy and Lactation Labeling Rule (PLLR). As a result of these revisions, modifications to the MG were also made.

A review of the proposed PLLR language was completed by Pharmacology/Toxicology on July 17, 2019, and Division of Pediatric and Maternal Health on August 30, 2018.

A Clinical Pharmacology review of the drug-drug interaction information, and proposed labeling revisions, was completed September 20, 2018.

Proposed revised labeling was sent to the firm on March 22, 2019, and the firm stated that the labeling was acceptable.

Up to this point in time, the supplement was managed by Jennifer Johnson, but I was asked to take this application to an approval action.

Review

Prescribing Information (PI)

The labeling sent to the firm on March 22, 2019, was compared to the currently approved PI (Approved May 16, 2017 in S-007). The firm has not made any additional revisions to the labeling other than those pertaining to this current supplement.

The labeling sent back to the firm on October 23, 2019, was the identical labeling the firm had previously found acceptable, revised as follows:

1. The text in RECENT MAJOR CHANGES was deleted since those revisions occurred over 1 year ago.

Medication Guide (MG)

The labeling sent to the firm on March 22, 2019 was compared to the currently approved MG (Approved May 16, 2017 in S-007). No other revisions were made to the labeling other than those pertaining to this current supplement. In the labeling sent back to the firm on October 23, 2019, I made the following revisions:

Under" **Do not take Korlym if you are taking",** I deleted "Juvisync", "Simcor" (both mentioned with simvastatin) and "Advicor" (listed with lovastatin) as they are no longer marketed. I also corrected the spelling of "Neudexta" (listed under quinidine) to "Nuedexta".

The firm responded, on October 24, 2019, to the labeling sent to them on October 23, 2019. The firm sent the following responses to our revisions (responses are underlined):

-Removed RECENT MAJOR CHANGES as they are over 1 year old
Thank you. This makes sense. Question – the changes to this label update include dosing pertaining to concomitant administration with strong CYP3A inhibitors (increased dose from do not exceed 600 mg once daily to do not exceed 900 mg once daily, and all changes related to compliance with the PLLR. Should we replace the removed text with "Dosage and Administration (2.5) and the date of this label (assume 10/2019)?

-In the MG under **Do not take KORLYM if you are taking:** I have removed the following products as they are no longer marketed:
Juvisync, Simcor, Advicor
Juvisync (simvastatin; sitagliptin phosphate) oral tablets; Application holder N202343: Merck Sharp and Dome Corp has been discontinued
According to the DailyMed, both Simcor and Advicor (labels attached) are still available and marketed by Physicians Total Care, Inc.
Therefore, we will remove Juvisync only from the Medication Guide.

I could not find approved NDAs for the following drugs, so if you could check to see if they are still marketed, I would appreciate it:
Gengraf, Migergot,
Both Gengraf and Migergot are still listed on DailyMed

Gengraf (cyclosporine) oral solution and capsule is listed by AbbVie Inc. The 25 mg and 100 mg are available; the 50 mg strength has been discontinued.
ANDA 065003 – Original approval 05/12/2000

Migergot (ergotamine tartrate and caffeine) suppository is listed by both Cosette Pharmaceuticals, Inc. and Horizon Pharma Inc.
ANDA 086557 – Original approval 10/04/1983 Cosette

Also, in this same list, NUEDEXTA is incorrectly spelled N**EU**DEXTA, so please correct that.
Nuedexta is the correct spelling per the DailyMed listing. See attached label. No correction needed.

The firm's responses are acceptable. It was determined that the revisions to the DOSAGE AND ADMINISTRATION section re: concomitant use with strong CYP3A inhibitors should be included in RECENT MAJOR CHANGES.

The labeling that was sent back to the firm on October 25, 2019, the firm's responses above were taken into consideration. Only Juvisync was removed from the MG. RECENT MAJOR CHANGES was added in citing the revision to the Dosage and Administration section. Vertical lines were placed to the left of text that was revised.

The firm sent back labeling on November 1, 2019. It was identical to the labeling sent to them on October 25, 2019, with the following exceptions:

HIGHLIGHTS OF PRESCRIBING INFORMATION
- Under RECENT MAJOR CHANGES, Dosage and Administration, changed section in parentheses to 2.5
- Under CONTRAINDICATIONS, 4th bullet, deleted extra "women with"
- Changed Revised date to 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*
- Under SECTION 2 DOSAGE AND ADMINISTRATION, added new subsection 2.1 Testing Prior to and During KORLYM Administration, and changed subsequent subsection numbering.

4 CONTRAINDICATIONS
- 4th bullet, deleted extra "women with"

Medication Guide

- Under Do not take KORLYM if you: are taking:, deleted extra comma between Vytorin® and Simcor®

Medication Guide

- Changed copyright to 2019
- Changed Revised date to 11/2019

Note: These are acceptable editorial revisions.

Recommendations

An Approval should be drafted.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATI JOHNSON
11/05/2019 12:55:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 08-29-2018

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Metabolic and Endocrine Products

Drug: Korlym (mifepristone) 300 mg tablets
NDA 202107/S-008

Applicant: Corcept Therapeutics, Inc.

Approved Indication: 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

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Labeling Conversion submitted as a Prior Approval Labeling Supplement

Materials Reviewed:
- Applicant's proposed labeling and supporting safety review
- Approved Korlym labeling (05-16-2017)
- Literature review

Consult Question: Please review the Pregnancy and Lactation Labeling Rule (PLLR) Labeling

INTRODUCTION

The applicant submitted a Prior Approval Labeling Supplement for Korlym (mifepristone) on 3-30-2018 that included a Pregnancy and Lactation Labeling Rule (PLLR) labeling conversion, in addition to revisions of other sections of labeling. The Division of Metabolism and Endocrinology Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on 6-1-2018, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

Korlym (mifepristone) is a cortisol receptor blocker that was approved in 2012 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. Mifepristone is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses. The approved dose is 300 mg daily, which may be increased up to 1200 mg daily. Mifepristone is approved, under the trade name Mifeprex, for pregnancy termination, in a regimen with misoprostol (mifepristone followed by misoprostol 24-48 hours later); the original approval was a 600 mg single dose, which was revised to a single 200 mg dose in 2016.

Drug characteristics include the following:

- half-life 85 hours; half-life of a single dose of 200 mg or 600 mg is 12-72 hours at first, then 18 hours[1]
- molecular weight 429.6 Daltons
- serious adverse reactions include
    - adrenal insufficiency
    - hypokalemia
    - endometrial changes (thickening) and vaginal bleeding.

Current State of the Labeling (5-16-2017)

Currently approved Korlym labeling is in the Physician Labeling Rule (PLR) format. DPMH provided labeling recommendations during the original NDA review cycle.[2] The following information is included in currently approved labeling:

- Boxed Warning regarding termination of pregnancy
- Contraindication in pregnancy

Warnings and Precautions

- Vaginal bleeding and endometrial changes (also included in 6.1 Clinical Trials Experience)

[1] Based on Mifeprex labeling (3-29-2016)

[2] See review by Dr. Upasana Bhatnagar in DARRTS, dated 2-14-2012

8.1 Pregnancy
- Pregnancy category X
- Human data: in a report of 13 live births after single dose mifepristone exposure, no fetal abnormalities were noted
- Animal Data: increased fetal losses in rabbits at doses less than human exposure at the maximum clinical dose, based on body surface area; skull deformities in rabbits at less than human exposure, most likely due to uterine contractions resulting from antagonism of the progesterone receptor.

8.3 Nursing Mothers
- A statement that mifepristone is present in human milk, and that because of the potential for serious adverse reactions, a decision should be made to discontinue nursing or discontinue the drug.

8.8 Females of Reproductive Potential
- A recommendation to exclude pregnancy
- Non-hormonal contraception recommendation

Cushing's Syndrome in Pregnancy
- Cushing's syndrome (CS) is rare in pregnancy as hypercortisolism is associated with anovulatory infertility[3]
- A published review of 220 cases of pregnant women with CS reported in the literature showed limited experience in pregnancy:[3]
    - most common cause: adrenal adenoma
    - no established treatment guidelines (the following have been reported: second trimester surgical resection of adenomas and off-label medical management with metyrapone, a diagnostic drug for testing hypothalamic-pituitary ACTH function, that reduces adrenal cortisol production)[4]
    - association with adverse maternal outcomes (gestational diabetes, pre-eclampsia) and fetal outcomes (fetal loss, preterm birth).

REVIEW OF DATA

Pregnancy
Nonclinical Experience

No additional reproductive and developmental nonclinical studies were conducted for this submission. Please refer to the PLLR Nonclinical review by Dr. Patty Brundage.

[3] Caimari F, Valassi E, Garbayo P, et al. Cushing's syndrome and pregnancy outcomes: a systematic review of published cases. Endocrine (2017) 55: 555-563.

[4] Nieman L, Biller B, Findling J, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. The J of Clinical Endocrinology & Metabolism 2015. Vol 100, Issue 8:2807-2831.

Review of Human Pregnancy Data

Applicant's literature review
The applicant's review of the published literature includes outcome data on pregnancies exposed to single dose mifepristone for pregnancy termination: (see Table 1 in the Appendix for a summary)

- A prospective, multicenter, observational study in France assessed outcomes in women who changed their mind about pregnancy termination (following exposure to mifepristone alone (n=46)) or had a failed termination (following exposure to mifepristone with misoprostol (n=59)) during the first 12 weeks of pregnancy.[5] A 4.2% major birth defect rate (95% CI, 1.2% to 10.4%) was reported among the 94 live births. This rate is higher than the 2% to 3% rate of major birth defects among the general population of France. The rate of miscarriage was 9.6%. There was no pattern of birth defects, and one birth defect in the mifepristone alone exposed group consisted of Horner syndrome in a large for gestational age neonate. The authors noted that Horner syndrome may have been caused by trauma during delivery. Additionally the authors noted that concomitant misoprostol exposure probably contributed to the birth defect cases, as misoprostol exposure in pregnancy has been associated with birth defects, including Mobius sequence and transverse limb defects.[6]

- Case series and case reports that included no pattern of malformations.[7,8,9,10,11]

Reviewer Comments
There are no data on long term exposure to mifepristone for management of Cushing's syndrome during pregnancy. Available data are based on a small study of 46 exposures to a single dose of mifepristone and case reports, which are limited by the lack of denominator data and lack of clinical details on comorbidities, concomitant exposures, and outcomes. It is not possible to draw meaningful conclusions from these data as data based on exposure to a single dose of

[5] Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG 2013; 120:568-575.

[6] Da Silva Dal Pizzol T, Knop FP, Mengue SS. Prenatal exposure to misoprostol and congenital anomalies: Systematic review and meta-analysis. Reprod Toxicol 2006; 22:666-671.

[7] Sitruk-Ware R, Davey A, Sakiz E. Fetal malformation and failed medical termination of pregnancy. Lancet 1998; 352:323.

[8] Sentilhes L, Patrier S, Chouchene S, Diguet A, Berthier A, Marpeau L, Verspyck E: Amniotic band syndrome with limb amputation after exposure to mifepristone in early pregnancy. Fetal Diagn Ther 22(1):51-54, 2007.

[9] Sorensen ECH et al. Failed medical termination of twin pregnancy with mifepristone: a case report. Contraception 71 (2005) 231-233. 2005.

[10] Pons J-C, Imbert M-C, Elefant E, Roux C, Herschkorn P, Papiernik E: Development after exposure to mifepristone in early pregnancy. Lancet 338(8769):763, 1991

[11] Lim et al. Normal development after exposure to mifepristone in early pregnancy. Lancet 336:257-8, 1990.

mifepristone is not helpful to inform the risk of long term exposure for management of Cushing's syndrome.

DPMH Literature Review
DPMH performed a search of published literature on mifepristone exposure in pregnancy, and did not identify any additional publications.

Review of Pregnancy related Pharmacovigilance Database
The applicant's cumulative safety database review through a cut-off date of 7-24-2018, includes 3 pregnancy related reports following exposure to Korlym:

- spontaneous abortion n=2
- outcome unknown n=1.

Applicant's Conclusion
The applicant concluded that there is no new safety information on the use of Korlym during pregnancy. The applicant proposed the addition of available published mifepristone data to labeling.

Reviewer Comment
DPMH concurs (see Summary discussion below).

Summary
Mifepristone is a selective antagonist of the progesterone receptor at low doses (200 mg-600 mg), and blocks the glucocorticoid receptor at higher doses (300 mg-1200 mg). Because the mifepristone dose in Korlym may result in pregnancy termination, approved labeling includes a boxed warning and contraindication regarding use in pregnancy. Available published data on mifepristone exposure during pregnancy are limited to one small study of exposure to a single dose of mifepristone for pregnancy termination (n=46) and case reports, and are insufficient to inform a risk of adverse developmental outcomes. The study showed a birth defect rate higher than the background population rate (4 % compared to 2-3%), but no pattern of defects. There are no data on long term exposure in pregnancy to treat Cushing's syndrome. Therefore, it is reasonable to include a risk summary statement in labeling that reflects this conclusion, and include available study results under the Human Data heading. Inclusion of data following exposure to a single dose of mifepristone may be informative for pregnant women who may have had inadvertent exposure to Korlym.

Lactation
Nonclinical Experience
No additional nonclinical studies were submitted with this labeling supplement.

Review of Human Lactation Data

Applicant's Literature Review

The applicant identified a published lactation study of 12 breastfeeding women who received a single dose of mifepristone for pregnancy termination 6-12 months post-partum.[12] Breastmilk samples were collected up to 7 days after taking mifepristone. Among the 10 women who received a single oral dose of 600 mg, milk concentrations were highest in the first samples collected during the first 12 hours after drug intake and ranged from undetectable (<5.6 mcg/L) to 392.2 mcg/L. In the 2 women who received a single oral dose of 200 mg, mifepristone was undetectable in breastmilk at all times.

The authors estimated that a fully breastfed infant would receive a relative infant dose (RID) of 0.5% (percent of the weight-adjusted maternal dose) following a single dose of 600 mg of mifepristone.

Women pumped and discarded their breastmilk for the first 3 days following intake of mifepristone. No infant adverse reaction data were reported.

DPMH Literature Review
DPMH conducted a search of *Medications and Mother's Milk*[13], the Drugs and Lactation Database (LactMed)[14], and of published literature. *Medications and Mother's Milk* states that based on the above published lactation study, "Limited Data-Probably Compatible" following pregnancy termination. LactMed states "Limited information indicates that breastfeeding need not be interrupted after a single dose of mifepristone." DPMH did not identify any additional published data.

Review of Pharmacovigilance Database
The applicant performed a review of their pharmacovigilance safety database for cases of mifepristone and lactation, and did not identify any reports.

Applicant's Conclusion
The applicant proposed the addition of available published data and the PLLR benefit-risk statement to labeling.

Reviewer Comment
DPMH concurs (see Summary discussion below).

Summary
There is no information on the amount of mifepristone in human milk, the effects on breastfed infants, or the effects on milk production during long term use of mifepristone. Available data

[12] Saav I, Fiala C, Hamaleinen JM, Heikinheimo O, Gemzell-Danielsson K. Medical abortion in lactating women – low levels of mifepristone in breast milk. Acta Obstetricia et Gynecologica. 2010; 89: 618–622.

[13] Hale, Thomas (2018) Medications and Mothers' Milk online

[14] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine database that reviews available information on drug levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

based on intake of a single dose of mifepristone showed a small amount in breastmilk. These data may underestimate the amount of mifepristone in breast milk as this study was conducted in women who were 6-12 months postpartum, and the publication does not report whether the women were exclusively breastfeeding. Additionally, the half-life of misoprostol is longer with long term dosing compared to a single dose; therefore, exposure may be greater with long term use. It is reasonable to include such a statement in the risk summary, to include the PLLR benefit-risk statement, and to include a statement that to minimize exposure to a breastfed infant, women who discontinue or interrupt Korlym treatment may consider pumping and discarding milk during treatment and for 18-21 days after the last dose, before breastfeeding.

Females and Males of Reproductive Potential

Nonclinical Experience

Section 13 of currently approved labeling includes nonclinical data that showed no infertility effects. No additional nonclinical studies were submitted with this application.

Review of Data

Applicant's Literature Review

The applicant identified a published study (b) (4) (b) (4) In 8 women who were given mifepristone 25 mg daily on days 1-14 and 1-21 of the menstrual cycle, serum estradiol levels were low during treatment, and returned to normal after discontinuation.

Another published study (b) (4) (b) (4) In 32 women who were given mifepristone 25-100 mg for 4 days starting on the 4th day of the luteal phase (based on identification of ovulation by basal body temperature shift and ultrasound of the ovaries), bleeding and premature luteal regression occurred in most women.

Reviewer Comment

These data are not sufficient to support an association between mifepristone use and infertility.

DPMH Literature Review

DPMH performed a search of published literature on mifepristone and infertility, and did not identify any publications.

Review of Pharmacovigilance Database

The applicant performed a review of their pharmacovigilance safety database for cases of mifepristone and infertility, and identified 7 reports of various nonspecific reproductive problems such as polycystic ovarian syndrome. No infertility cases were identified.

(b) (4)

Applicant's Conclusion
The applicant proposes [redacted] (b) (4)

Reviewer Comment
DPMH does not agree [redacted] (b) (4) .

Summary
Recommendations for pregnancy testing and contraception use that are in currently approved labeling will be moved to the Females and Males of Reproductive Potential subsection.

There are insufficient data to support an association with infertility [redacted] (b) (4) (b) (4)

CONCLUSION
The Pregnancy and Lactation subsections of Korlym labeling were structured to be consistent with the PLLR. DPMH has the following recommendations for the Korlym labeling:

- **8.1 Pregnancy**
  - The "Pregnancy" subsection of Korlym labeling was formatted in the PLLR format to include:
    - "Risk Summary"
    - "Data"
- **8.2 Lactation**
  - The "Lactation" subsection of Korlym labeling was formatted in the PLLR format to include the "Risk Summary", "Clinical Considerations", and "Data" headings

- **8.3 Females and Males of Reproduction**
  - The Females and Males subsection was added to Korlym labeling to include:
    - "Pregnancy Testing"
    - "Contraception".

DPMH LABELING RECOMMENDATIONS
DPMH recommendations are below. **See final labeling for all of the labeling revisions negotiated with the applicant.**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
KORLYM is contraindicated in pregnancy because the use of KORLYM results in pregnancy loss. There are no data that assess the risk of birth defects in women exposed to KORLYM during pregnancy. Available data limited to exposure following a single dose of mifepristone

during pregnancy showed a higher rate of major birth defects compared to the general population comparator (s*ee Data)*. In animals, pregnancy loss occurred in several species and fetal skull defects occurred in rabbits at below clinical doses *(see Data)*. The inhibition of both endogenous and exogenous progesterone by mifepristone at the progesterone receptor results in pregnancy loss. Advise pregnant women of the potential risk to a fetus. *[See Contraindications (4.1)]*

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

There are no data on long term exposure to mifepristone in pregnancy. Available data are limited to exposure to a single dose of mifepristone for pregnancy termination. In a prospective study in France of 46 pregnancies exposed to a single dose of mifepristone and 59 pregnancies exposed to a single dose of mifepristone and misoprostol, the overall major birth defect rate (4%) was greater than the general background rate of 2 to 3% (2 birth defects in each group). There was no pattern of birth defects identified.

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 mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from antagonism of the progesterone receptor.

8.2 Lactation

Risk Summary

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 *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KORLYM and any potential adverse effects on the breastfed child from KORLYM or from the underlying maternal condition.

Clinical Considerations

To minimize exposure to a breastfed infant, women who discontinue or interrupt KORLYM treatment may consider pumping and discarding milk during treatment and for 18-21 days after the last dose, before breastfeeding.

Data

Available data based on intake of a single dose of 600 mg of mifepristone in 10 breastfeeding women who were 6-12 months postpartum showed a small amount in breast milk (the estimated

relative infant does was 0.5%). The half-life of mifepristone is longer with repeat dosing compared to a single dose; therefore, there may be greater exposure with long term use.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Due to its anti-progestational activity, KORLYM causes pregnancy loss. Perform pregnancy testing before the initiation of treatment with KORLYM or if treatment is interrupted for more than 14 days in females of reproductive potential.

Contraception

Recommend non-hormonal contraception for the duration of treatment and for one month after stopping treatment. KORLYM interferes with the effectiveness of hormonal contraceptives. *[See Drug Interactions (7.6)]*

17 PATIENT COUNSELING INFORMATION

17.1 Importance of Preventing Pregnancy

- Advise patients that KORLYM will cause termination of pregnancy. KORLYM is contraindicated in pregnant patients.
- KORLYM reduces the effectiveness of hormonal contraceptives. 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.

Appendix I

Table 1 Summary of Published Data on Single dose Mifepristone (for Termination) Exposure in Pregnancy

Data Source	Number exposed	Comparator number	Findings	Comments
Prospective Observational Study (France)[17]	46 mifepristone alone 59 mifepristone + misoprostol	none	Major birth defect rate 4.2% (95% CI, 1.2% to 10.4%)	Major birth defect rate higher than background rate of 2-3% in France; confounding due to concomitant exposure to misoprostol; No pattern of birth defects
Manufacturer case series[18]	21 mifepristone (m) alone 50 mifepristone + prostaglandin analog (m+p)	none	1/21 m exposed with multiple anomalies: sirenomelia, cleft lip and palate, 7 toes, hypoplastic lungs, absence of reproductive organs, lower urinary tract and kidney 7/50 m+ p exposed major birth defects: anencephaly, heart malformation, cerebellum atrophy, talipes equinovarus (n=4)∗, finger nail defect	
Case report[19]	1	none	Amniotic band syndrome with limb amputation, talipes, cerebellum atrophy	

[17] Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG 2013; 120:568-575.

[18] Sitruk-Ware R, Davey A, Sakiz E. Fetal malformation and failed medical termination of pregnancy. Lancet 1998; 352:323.

[19] Sentilhes L, Patrier S, Chouchene S, Diguet A, Berthier A, Marpeau L, Verspyck E: Amniotic band syndrome with limb amputation after exposure to mifepristone in early pregnancy. Fetal Diagn Ther 22(1):51-54, 2007.

Data Source	Number exposed	Comparator number	Findings	Comments
Case report[20]	1	none	Normal newborn	
Case report[21]	1	none	Normal newborn	
Case reports[22]	3	none	Normal newborn	

∗ One newborn had anencephaly and talipes and was counted as 1 birth defect case out of 50 pregnancies exposed to mifepristone and a prostaglandin analog.

[20] Sorensen ECH et al. Failed medical termination of twin pregnancy with mifepristone: a case report. Contraception 71 (2005) 231-233. 2005.

[21] Pons J-C, Imbert M-C, Elefant E, Roux C, Herschkorn P, Papiernik E: Development after exposure to mifepristone in early pregnancy. Lancet 338(8769):763, 1991.

[22] Lim et al. Normal development after exposure to mifepristone in early pregnancy. Lancet 336:257-8, 1990.

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/s/

LEYLA SAHIN
08/29/2018

LYNNE P YAO
08/30/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: Sue Rinne
To: Johnson, Kati
Subject: Re: NDA 202107, Korlym, pending S-008 (b) (4) revisions to labeling sent to firm on 3.22.2019
Date: Wednesday, October 23, 2019 11:32:36 AM

Dear Kati,

Understood.

Thank you,
Sue

Sent from my iPhone

> On Oct 23, 2019, at 8:16 AM, Johnson, Kati <Kati.Johnson@fda.hhs.gov> wrote:
>
> Sorry Sue, this is revised labeling for S-008 ONLY.
>
> Kati Johnson
> Senior Regulatory Project Manager
> Division of Metabolism and Endocrinology Products
> Office of Drug Evaluation II
> Phone: 301-796-1234
> Fax: 301-595-2123
>
> ---
>
> **From:** Johnson, Kati
> **Sent:** Wednesday, October 23, 2019 10:54 AM
> **To:** Sue Rinne <srinne@corcept.com>
> **Cc:** Johnson, Kati <Kati.Johnson@fda.hhs.gov>
> **Subject:** NDA 202107, Korlym, pending S-008 (b) (4) revisions to labeling sent to firm on 3.22.2019
>
> Hi Sue,
> **Please confirm receipt of this email.**
> I finally had time to review the labeling you had previously found acceptable.
> So sorry I am late with this email.
> I have made the following revisions in the attached labeling:
> -Removed RECENT MAJOR CHANGES as they are over 1 year old
> -In the MG under **Do not take KORLYM if you are taking:** I have removed the following products as they are no longer marketed:
> Juvisync, Simcor, Advicor

I could not find approved NDAs for the following drugs, so if you could check to see if they are still marketed, I would appreciate it:
Gengraf, Migergot,

Also, in this same list, NUEDEXTA is incorrectly spelled N**EU**DEXTA, so please correct that.

I went ahead and revised the Revision Date in HIGHLIGHTS to XX/XXXX. I can change that at the very end and it is considered "editorial" so I don't need to get your OK. I would like to get it approved this month but I am late in getting this to you plus I am not familiar with the clearance process for labeling revisions in the Endocrine Clinical group (I manage drug groups in the LIPID/OBESITY clinical group). I am off (b) (6) (b) (6) and I am hoping I can get it approved by then.

IF THE ATTACHED LABELING IS OK, JUST LET ME KNOW VIA EMAIL. NO NEED TO SEND THE LABELING BACK.
I have drafted the AP letter ☺
Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Phone: 301-796-1234
Fax: 301-595-2123

22 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATI JOHNSON
10/25/2019 11:55:34 AM

From:	Johnson, Kati
To:	Sue Rinne
Subject:	FW: NDA 202107, Korlym, pending S-008 (b) (4), revisions to labeling sent to firm on 3.22.2019
Date:	Friday, October 25, 2019 3:13:00 PM
Attachments:	201207 S008 (b) (4) .22. revised to firm 10.23.doc Simcor label.pdf Advicor.pdf Nuedexta.pdf 201207 S008 labeling from firm 10.24 revised 10.25 to firm.doc

Hi Sue,
I think we are done. I took your PI sent back to me on 10/24 and revised it to:
-Add revisions to D&A in RMC
-took your revisions to the list of approved drugs. Thanks for looking into that
-I added the vertical lines to denote changed text
-I also changed the revision date in HL to 10/2019. I am that confident that we are done. Hopefully I didn't screw up ☺
Let me know if the labeling looks OK to you all.
OK to do this Monday. Have a good weekend.
If there are issues, let's chat vs. sending me back revised labeling.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Phone: 301-796-1234
Fax: 301-595-2123

From: Sue Rinne <srinne@corcept.com>
Sent: Thursday, October 24, 2019 3:51 PM
To: Johnson, Kati <Kati.Johnson@fda.hhs.gov>
Subject: FW: NDA 202107, Korlym, pending S-008 (b) (4), revisions to labeling sent to firm on 3.22.2019

Hi Kati,

Thank you for the comments. I have inserted in blue/bold font questions and responses within your text below.
We can revise the label and send our agreed upon redline after we receive your response to this message, if that works for you.

Best regards,
Sue

Susan Rinne
Vice President, Corporate Regulatory Affairs

Corcept Therapeutics
149 Commonwealth Drive
Menlo Park, CA 94025
Ph 650.688.8784 / Cell (b) (6) */ Fax 650.327.3218*

From: Johnson, Kati <Kati.Johnson@fda.hhs.gov>
Sent: Wednesday, October 23, 2019 7:54 AM
To: Sue Rinne <srinne@corcept.com>
Cc: Johnson, Kati <Kati.Johnson@fda.hhs.gov>
Subject: NDA 202107, Korlym, pending S-008 (b) (4) revisions to labeling sent to firm on 3.22.2019

Hi Sue,
Please confirm receipt of this email.
I finally had time to review the labeling you had previously found acceptable.
So sorry I am late with this email.
I have made the following revisions in the attached labeling:
-Removed RECENT MAJOR CHANGES as they are over 1 year old
Thank you. This makes sense. Question – the changes to this label update include dosing pertaining to concomitant administration with strong CYP3A inhibitors (increased dose from do not exceed 600 mg once daily to do not exceed 900 mg once daily, and all changes related to compliance with the PLLR. Should we replace the removed text with "Dosage and Administration (2.5) and the date of this label (assume 10/2019)?

-In the MG under **Do not take KORLYM if you are taking:** I have removed the following products as they are no longer marketed:
Juvisync, Simcor, Advicor
Juvisync (simvastatin; sitagliptin phosphate) oral tablets; Application holder N202343: Merck Sharp and Dome Corp has been discontinued
According to the DailyMed, both Simcor and Advicor (labels attached) are still available and marketed by Physicians Total Care, Inc.
Therefore, we will remove Juvisync only from the Medication Guide.

I could not find approved NDAs for the following drugs, so if you could check to see if they are still marketed, I would appreciate it:
Gengraf, Migergot,
Both Gengraf and Migergot are still listed on DailyMed

Gengraf (cyclosporine) oral solution and capsule is listed by AbbVie Inc. The 25 mg and 100 mg are available; the 50 mg strength has been discontinued.
ANDA 065003 – Original approval 05/12/2000

Migergot (ergotamine tartrate and caffeine) suppository is listed by both Cosette Pharmaceuticals, Inc. and Horizon Pharma Inc.
ANDA 086557 – Original approval 10/04/1983 Cosette

Also, in this same list, NUEDEXTA is incorrectly spelled N**EU**DEXTA, so please correct that.
Nuedexta is the correct spelling per the DailyMed listing. See attached label. No correction needed.

I went ahead and revised the Revision Date in HIGHLIGHTS to XX/XXXX. I can change that at the very end and it is considered "editorial" so I don't need to get your OK. I would like to get it approved this month but I am late in getting this to you plus I am not familiar with the clearance process for labeling revisions in the Endocrine Clinical group (I manage drug groups in the LIPID/OBESITY clinical group). I am (b) (6) and I am hoping I can get it approved by then.

IF THE ATTACHED LABELING IS OK, JUST LET ME KNOW VIA EMAIL. NO NEED TO SEND THE LABELING BACK.
I have drafted the AP letter ☺
Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Phone: 301-796-1234
Fax: 301-595-2123

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/s/

KATI JOHNSON
10/25/2019 06:14:53 PM

From:	Johnson, Jennifer
To:	"Sue Rinne"
Cc:	Lucarelli, Pamela K
Bcc:	Johnson, Jennifer
Subject:	NDA 202107 (Korlym): FDA comments on S-008 and (b) (4)
Date:	Friday, March 22, 2019 4:59:00 PM
Attachments:	NDA 202107 S008 FDA edits.doc NDA 202107 (b) (4) FDA comments.doc

Hi Sue,

We have reviewed the latest proposed Korlym labeling for pending S-008 (PLLR conversion, addition of DDI study information) (b) (4) Please find attached our edits and comments. I have kept the proposed PIs for the two supplements separate for ease of review.

If you could respond by Wednesday, April 3rd, we would appreciate it. An email response is sufficient for now.

Let us know if you have any questions. Thank you for your patience.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
03/22/2019 05:07:13 PM

From: Johnson, Jennifer
To: "Sue Rinne"
Bcc: Johnson, Jennifer
Subject: NDA 202107/S-008 (Korlym): FDA edits
Date: Monday, October 01, 2018 6:17:00 PM
Attachments: FDA edits nda-202107-proposed-pi-clean-response-30mar-redline-v2.doc

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Hi Sue,

Please find attached the Korlym PI which includes our edits, and let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Sue Rinne <srinne@corcept.com>
Sent: Friday, September 28, 2018 7:09 PM
To: Johnson, Jennifer <Jennifer.Johnson@fda.hhs.gov>
Subject: Re: NDA 202107/S-008

Hi Jennifer,

Received your email. Thanks for letting me know. Will look for your email next week.

Best regards,
Sue

Sent from my iPhone

On Sep 28, 2018, at 4:05 PM, Johnson, Jennifer <Jennifer.Johnson@fda.hhs.gov> wrote:

> Hi Sue,
>
> I'm sorry for the delay. We won't be meeting the goal date, but plan on wrapping this one up soon.
> I anticipate sending you a draft with some edits on Monday.
> Thanks for your patience!

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

From: Sue Rinne <srinne@corcept.com>
Sent: Thursday, September 27, 2018 4:30 PM
To: Johnson, Jennifer <Jennifer.Johnson@fda.hhs.gov>
Subject: NDA 202107/S-008

Hi Jennifer,

You are probably expecting my question on whether we will be hearing regarding our Korlym labeling supplement 008 this week?

Many thanks.

Best regards,
Sue

Susan Rinne
Vice President, Corporate Regulatory Affairs
Corcept Therapeutics
149 Commonwealth Drive
Menlo Park, CA 94025
Ph 650.688.8784 / Cell (b) (6) */ Fax 650.327.3218*

44 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

JENNIFER L JOHNSON
10/01/2018