

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202107Orig1s007

Trade Name: KORLYM

Generic or Proper Name: mifepristone

Sponsor: Corcept Therapeutics, Inc.

Approval Date: May 16, 2017

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

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APPROVAL LETTER



NDA 202107/S-007

SUPPLEMENT APPROVAL

Corcept Therapeutics Incorporated
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 2, 2017, and your amendment, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Korlym (mifepristone) tablets, 300 mg.

We also refer to our letter dated February 3, 2017, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Korlym. This information pertains to the risk of increased mifepristone exposure when Korlym is administered concomitant with CYP3A inhibitors, based on new safety information about this risk identified since the product was approved.

This supplemental new drug application provides for revisions to the labeling for Korlym, consistent with our February 3, 2017, letter.

We note that the final proposed labeling submitted via email on May 15, 2017, is consistent with the above letter and the labeling comments sent to you on March 23 and April 11, 2017.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below and indicated in the enclosed labeling.

- Addition of "Recent Major Changes" to the Highlights section and corresponding margin marks in the Full Prescribing Information.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, Medication Guide) with the addition of any labeling changes in pending “Changes Being Effectuated” (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 titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications 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 MS Word format, that includes the changes with the revisions indicated above approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, 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, 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(s) 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 package insert(s) 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 Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), 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

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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, please call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER R PIPPINS
05/16/2017

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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 antiprogesterone 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 (2.4) 05/2017
Warnings and Precautions (5.6) 05/2017

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

- Administer once daily orally with a meal (2.1).
- The recommended starting dose is 300 mg once daily (2.1).
- 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 (2.1).
- Renal impairment: do not exceed 600 mg once daily (2.2).
- Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment (2.3).
- Concomitant administration with strong CYP3A inhibitors: Do not exceed 600 mg once daily (2.4).

DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg (3)

CONTRAINDICATIONS

- Pregnancy (4.1, 8.1)
- Use of simvastatin or lovastatin and CYP3A substrates with narrow therapeutic range (4.2)
- Concurrent long-term corticosteroid use (4.3)

- Women with history of unexplained vaginal bleeding (4.4)
- Women with endometrial hyperplasia with atypia or endometrial carcinoma (4.4)

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 600 mg (5.6).

ADVERSE REACTIONS

Most common adverse reactions in Cushing's syndrome ($\geq 20\%$): 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 600 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).

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2017

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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 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.

2.2 Dosing in Renal Impairment

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

2.3 Dosing in Hepatic Impairment

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

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 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

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
1200 mg	Reduce dose to 600 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

4.1 Pregnancy

KORLYM is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with KORLYM or if treatment is interrupted for more than 14 days in females of

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reproductive potential. Non-hormonal contraceptives should be used during and one month after stopping treatment in all women of reproductive potential. [See *Use in Specific Populations* 8.8]

4.2 Drugs Metabolized by CYP3A

KORLYM is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, 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)]

4.3 Corticosteroid Therapy Required for Lifesaving Purposes

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

4.4 Women with Risk of Vaginal Bleeding or Endometrial Changes

KORLYM is contraindicated in the following:

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

4.5 Known Hypersensitivity to Mifepristone

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

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Insufficiency

Patients receiving mifepristone may experience adrenal insufficiency. Because serum cortisol levels remain elevated and may even increase during treatment with KORLYM, serum cortisol levels do not provide an accurate assessment of 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 600 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.

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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 $\geq 20\%$ 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 $\geq 10\%$ 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 $\geq 10\%$ 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 $\geq 5\%$ 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 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)]

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category X

KORLYM is contraindicated in pregnancy. KORLYM can cause fetal harm when administered to a pregnant woman because the use of KORLYM results in pregnancy loss. The inhibition of both endogenous and exogenous progesterone by mifepristone at the 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 (4.1)*]

Human Data

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

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area) were carried out. Because of the anti-progestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at less than human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from antagonism of the progesterone receptor.

8.3 Nursing Mothers

Mifepristone is present in human milk of women taking the drug. Because of the potential for serious adverse reactions in nursing infants from KORLYM, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of KORLYM in pediatric patients have not been established.

8.5 Geriatric Use

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

8.6 Renal Impairment

The maximum dose should not exceed 600 mg per day in renally impaired patients. [See *Clinical Pharmacology (12.3)*]

8.7 Hepatic Impairment

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

8.8 Females of Reproductive Potential

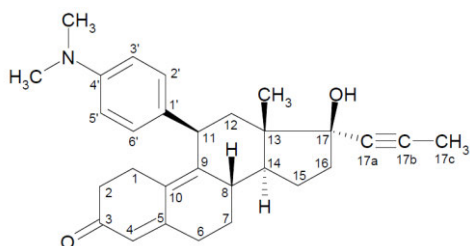
Due to its anti-progestational activity, KORLYM causes pregnancy loss. Exclude pregnancy before the initiation of treatment with KORLYM or if treatment is interrupted for more than 14 days in females of reproductive potential. Recommend contraception for the duration of treatment and for one month after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

10 OVERDOSAGE

There is no experience with overdose of KORLYM.

11 DESCRIPTION

KORLYM (mifepristone) is a cortisol receptor blocker for oral administration. The chemical name of mifepristone is 11 β -(4-dimethylaminophenyl)-17 β -hydroxy-17 α -(1-propynyl)-estra-4, 9-dien-3-one. The chemical formula is C₂₉H₃₅NO₂; 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 μ M) 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 $\geq$ 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	15.70	18.20
			simvastatin	10.40	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	1.80	0.81
			4-hydroxy-alprazolam	0.76	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	1.38	1.28
			Metabolite 1†	1.02	1.06

			Metabolite 2†	1.67	1.69
			Metabolite 3†	0.95	0.96
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, pimozone, 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/m² (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.
- 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: - o have a negative pregnancy test before starting KORLYM - o have a negative pregnancy test before restarting KORLYM if you stop taking it for more than 14 days - o 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: - o simvastatin (Zocor®, Vytorin®, Juvisync®, Simcor®) - o lovastatin (Mevacor®, Altoprev®, Advicor®) - o cyclosporine (Gengraf®, Neoral®, Restasis®, Sandimmune®) - o dihydroergotamine (Migranal®) - o ergotamine (Ergomar®, Migergot®) - o fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Sublimaze Preservative Free®, Subsys®) - o pimozone (Orap®) - o quinidine (Neudexta®) - o sirolimus (Rapamune®, Torisel®) - o tacrolimus (Prograf®, Protopic®) • must take corticosteroid medicines for other serious medical problems • are a woman who still has her uterus (womb) and have: - o unexplained bleeding from your vagina - o changes in the cells lining your uterus (endometrial hyperplasia) or cancer of the lining of your uterus (endometrial cancer) • are allergic to mifepristone or any of the ingredients in KORLYM. See the end of this Medication Guide for a complete list of ingredients in KORLYM. Talk to your doctor before taking KORLYM if you have any of these conditions.
What should I tell my doctor before taking KORLYM? Before taking KORLYM, tell your doctor if you: • have low potassium in your blood (hypokalemia) • have or have had a bleeding problem or are taking medicines to thin your blood • have or have had heart problems • have had an organ transplant have been taking medicines called corticosteroids (cortisone, dexamethasone, methylprednisolone, prednisolone, prednisone) • are breastfeeding or plan to breastfeed. KORLYM passes into your breast milk and may harm your baby. You and your doctor should decide if you will take KORLYM or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements. Using KORLYM with certain other medicines can affect each other. Using KORLYM with other medicines can cause serious side effects. Especially tell your doctor if you take: • medicines to treat: - o fungal infections (such as ketoconazole) - o depression - o HIV infection - o Hepatitis C infection - o certain bacterial infections - o 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?” • 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: - o unusual tiredness or weakness - o nausea - o fatigue - o low blood pressure (hypotension) - o 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: - o muscle weakness, aches, or cramps - o abnormal or irregular heartbeats (palpitations) • bleeding from the vagina. KORLYM may cause the lining of your uterus to become thick and may cause your uterus to bleed. Tell your doctor right away about any bleeding from your vagina that is not normal for you. • problems with the electrical system of your heart (QT interval prolongation). • worsening of symptoms of other medical problems that are treated with corticosteroids when you take corticosteroids and KORLYM at the same time. The most common side effects of KORLYM include: • nausea • headache • pain in your arms and legs (arthralgia) • fatigue • low potassium in your blood • vomiting	

• swelling of your arms and legs (peripheral edema) • dizziness • 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. ©2017 Corcept Therapeutics Incorporated. All rights reserved. K-00004 MAY 2017 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: 05/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202107Orig1s007

**CLINICAL PHARMACOLOGY
REVIEW(S)**

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	202107/S-007, Safety labeling Change – Labeling Supplement
Submission Date	March 02, 2017
Brand Name	Korlym
Generic Name	Mifepristone
Reviewer	Suryanarayana Sista, Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Corcept Therapeutics, Inc.
Formulation; Strength	Tablets; 300 mg
Indication	1. Korlym is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery

The sponsor submitted a safety labeling change (SLC) labeling supplement for their approved NDA for Korlym (Mifepristone).

Background

As part of a post-marketing requirement (PMR 1875-2) for the approval of mifepristone (Korlym, NDA 202107), the Sponsor submitted the results of a study (C-1073-36) entitled “A Phase 1, Open-label, Study in Healthy Subjects to Determine the Effect of 200 mg BID Ketoconazole on the Pharmacokinetics of a Concomitantly Administered 600 mg OD Oral Dose of Korlym® (mifepristone); and of this dose of Korlym on the Pharmacokinetics of Ketoconazole”.

The findings from this study showed that:

- The administration of 600 mg Korlym once daily with 200 mg ketoconazole twice daily resulted in a 28% increase in mifepristone C_{max} and a 38% increase in AUC_{0-24}
- The increased mifepristone exposures are approximately 15% less than the exposures observed following the highest labeled dose of Korlym (1200 mg daily).
- The mean increase in exposure to the hydroxylated metabolite, RU 42698, when co-administered with ketoconazole was 65.5%.
- The RU-42698 exposure was 18% higher than that following the highest labeled dose of Korlym. This increase in exposure over the highest labeled dose is unlikely to be clinically important.
- Co-administration with ketoconazole resulted in little change in exposure to the mono-demethylated metabolite, RU 42633, or di-demethylated metabolite, RU 42848.

Exposure to metabolites RU 42633 and RU 42848 when co-administered with ketoconazole were similar to or slightly lower than exposure following the highest labeled Korlym dose.

Based on the findings of this study, the Sponsor revised portions of the label as discussed below:

HIGHLIGHTS OF PRESCRIBING INFORMATION	
DOSAGE AND ADMINISTRATION	
	(b) (4)
WARNINGS AND PRECAUTIONS	
	(b) (4)
DRUG INTERACTIONS	
	(b) (4)
2.4 Concomitant administration with CYP3A Inhibitors	
	(b) (4)

5.6 Use of Strong CYP3A Inhibitors

(b) (4)

7.2 CYP3A Inhibitors

(b) (4)

12.3 Pharmacokinetics

Drug-Drug Interactions

In Vivo Assessment of Drug Interactions

(b) (4)

(b) (4)

The Sponsor provided a justification document providing explanation for the proposed changes indicated above. The Sponsor's justifications and reviewer comments are discussed below:

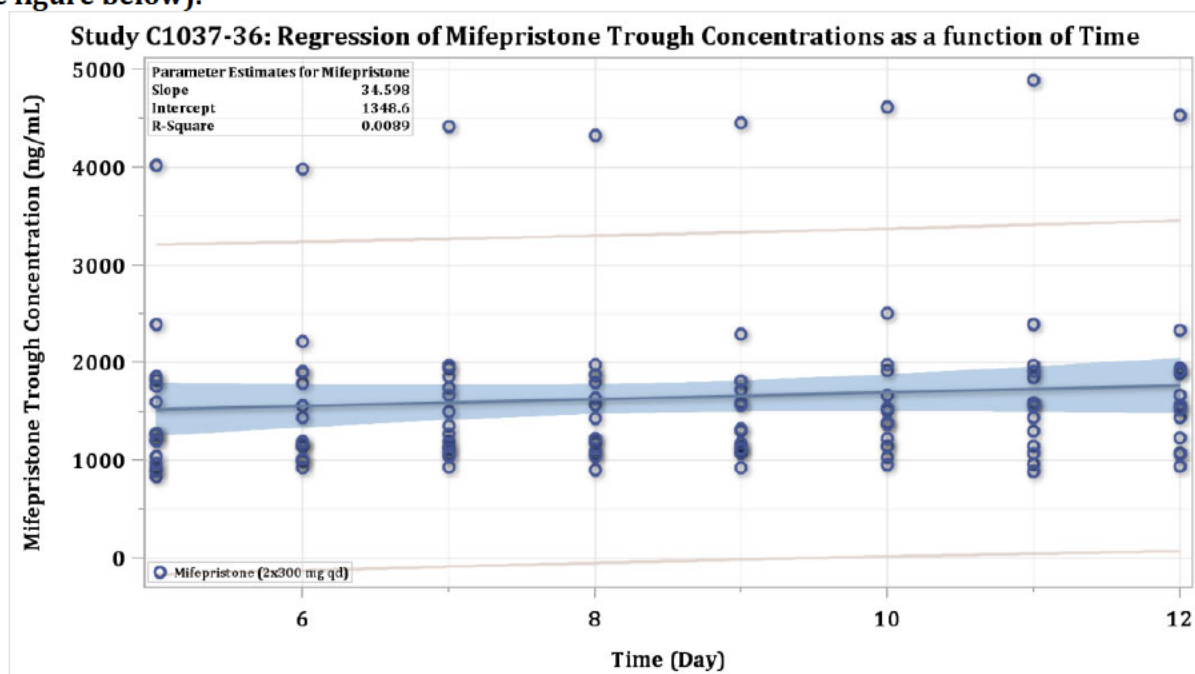
Sponsor's Position and Reviewer Comments:

Sponsor's Position:

1. The study C1073-36 results may have actually overestimated the effect of CYP3A inhibition since trough concentrations of mifepristone and RU42848 were still increasing day-by-day up to the start of ketoconazole administration on Day 13 (black circles □; Figure 1). This indicates that steady state conditions had not been attained at the time of ketoconazole administration, so that some of the increase in mifepristone exposure from Days 13-17 was likely due to continued accumulation of mifepristone independent of inhibition of CYP3A.

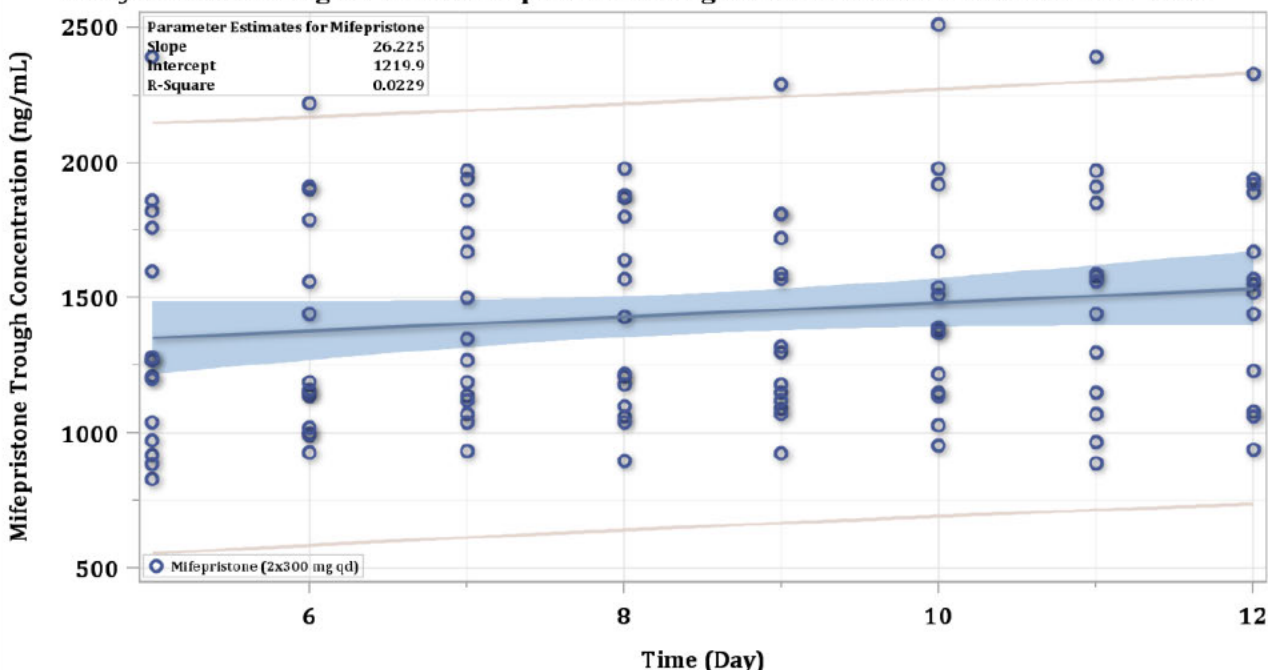
Reviewer Comments:

Mifepristone exhibits mechanism-based inhibition of its own metabolism. It is theoretically possible that there is continued accumulation of mifepristone independent of inhibition of CYP3A through days 13-17. However, contrary to the Applicant's position, it appears that steady state was attained by Day 12 (see figure below).



Excluding data from subject (b) (6) who had consistently high concentrations, did not change the outcome.

Study C1037-36: Regression of Mifepristone Trough Concentrations as a function of Time



Sponsor's Position :

2. With inhibition of CYP3A, the corresponding increases in C_{max} and AUC_{0-24h} (27.59% and 38.01%, respectively from Table 1) should yield systemic exposures similar in magnitude to those previously attained with 1200 mg daily (i.e., approximately the equivalent of $900 \cdot 1.38 = 1242$). This estimate is imprecise since 1.) across multiple pharmacokinetic studies with mifepristone, increases in C_{max} and AUC_{0-24h} are smaller than dose-proportional (Korlym NDA 202107 Module 2.7.2, Table 45), and 2.) the pharmacokinetic studies did not examine the dose-proportionality of daily doses of 900 and 1200 mg.

(b) (4)

The other key result from study C1073-36 was that CYP3A inhibition increases exposure to one of the three metabolites (RU 42698) to a larger magnitude than for mifepristone: 69% for C_{max} and 67% for AUC_{0-24h} . Both values are mid-way through the range of "weak" inhibition. Figure 1 shows that steady state conditions were attained for this metabolite prior to ketoconazole administration; therefore, the point estimates can be considered reliable. However, this metabolite is less potent than mifepristone at the glucocorticoid receptor (Table 2). As a result, this modest increase in exposure is likely less important compared to the even smaller increase in exposure to mifepristone.

However, the point estimate of 87% for GMR of the AUCs suggests exposure from 600 mg is on the low side,

(b) (4)

. Regardless, based on these calculations, the current 300-mg cap on daily dosing in subjects who require co-administration of a strong CYP3A inhibitor could compromise the clinical response in patients who previously benefitted from larger doses of Korlym.

Reviewer Comments:

In the absence of dose-proportionality, extrapolation of systemic exposures by multiplying a theoretical dose with the factor increase seen at a lower dose is unacceptable. Similar extrapolation of cross-study data shown in Sponsor's Table 3 would yield a test/reference geometric mean ratio of 130.91% for mifepristone AUC_{0-24h} at a dose of 900 mg ($87.27 \cdot (900/600)$), indicating a mean 31% increase (upper bound of 47.3%) in systemic exposure over that observed at the 1200 mg dose. This is in contrast to the 15% less exposure with the 600 mg dose compared to 1200 mg.

Following multiple dosing, the exposure of RU42633 is 1.28 folds compared to the parent, Mifepristone (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202107Orig1s000ClinPharmR.pdf). With a potency of 0.61 compared to the parent, and a 1.02 fold increase in exposure in presence of Ketoconazole, the total potency contribution of RU42633 would be 0.80 (1.28*0.61*1.02). Similarly the total potency contributions of RU42698 and RU42848 would be 0.38 and 0.36, respectively. As can be seen, the total potency of the metabolites when added together would exceed that of mifepristone.	
Sponsor's Position:	
3,	In summary, data from study C1073-36 show that mifepristone is an insensitive substrate for CYP3A, such that the effect of ketoconazole on mifepristone corresponds to what FDA defines as "weak" inhibition. (b) (4) [REDACTED]
Reviewer Comments:	
From the data shown in Table 3, the exposure following 600 mg mifepristone was in the range of the exposure seen with 1200 mg mifepristone. The impact of potential exposures (b) (4) when co-administered with a strong CYP3A4 inhibitor is not known. Based on the findings from this study, the Agency agrees to remove language regarding moderate CYP3A inhibitors from the product label. (b) (4) [REDACTED]. The dose of KORLYM should be limited to 600 mg, and strong inhibitors of CYP3A should be used only when necessary.	
Sponsor's Other Changes	
The Agency agrees with Sponsor's removal of mibefradil as an inhibitor from Section 2.4 and 7.2, since the product has been discontinued.	

The Agency recommended the following changes to the label:

HIGHLIGHTS OF PRESCRIBING INFORMATION	
DOSAGE AND ADMINISTRATION	
- Administer once daily orally with a meal (2.1). - The recommended starting dose is 300 mg once daily (2.1). - 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 (2.1). - Renal impairment: do not exceed 600 mg once daily (2.2). - Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment (2.3). - Concomitant administration with strong CYP3A inhibitors: Do not exceed 600 mg once daily (b) (4) [REDACTED] (b) (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 (b) (4) mg (5.6).

DRUG INTERACTIONS

- CYP3A inhibitors: Caution should be used when KORLYM is used with strong CYP3A inhibitors. Limit mifepristone dose to (b) (4) mg per day when used with strong CYP3A inhibitors (7.2).

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** (b) (4) should be used in combination with strong CYP3A inhibitors only when necessary. (b) (4)

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 (b) (4) should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to (b) (4) mg per day. [See Warnings & Precautions (5.4), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]

7.2 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 **KORLYM** mifepristone (b) (4)

(b) (4) 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 (b) (4) 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)]

12.3 Pharmacokinetics

Drug-Drug Interactions

In Vivo Assessment of Drug Interactions (see Table 2)

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 (b) (4)	1.38 1.02 1.67 0.95	1.28 1.06 1.69 0.96
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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
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*No effect = 90% CI within range 0.80 – 1.25

The Sponsor was notified on 23 March, 2017 of the Agency's assessment of the finding of the DDI study and its disagreement with the Sponsor's position. Agency recommended language, capping Korlym dose at 600 mg when co-administered with a strong CYP3A inhibitor, and additional suggested changes as indicated above, were sent to the Sponsor. In a response submission dated 30 March, 2017, the Sponsor added clarification language in Section 2.4 (shown below in highlighted text), and agreed to the rest of the Agency proposed changes, as shown below:

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 600 mg. (b) (4)

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
1200 mg	Reduce dose to 600 mg

12.3 Pharmacokinetics

Drug-Drug Interactions

In Vivo Assessment of Drug Interactions (see Table 3)

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† Metabolite 3†	1.67 0.95	1.69 0.96
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

The suggested addition of a clarification Table in Section 2.4, and clarification footer in Table 3 in Section 12.3 were acceptable to the Agency. The language (b) (4) in Section 2.4 was changed by the Agency to "Start at a dose of 300 mg. If clinically indicated, titrate to a maximum of 600 mg."

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/s/

SURYANARAYANA M SISTA
04/21/2017

JAYABHARATHI VAIDYANATHAN
04/21/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202107Orig1s007

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Metabolism and Endocrinology Products (DMEP)

Application: NDA 202107/S-007

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

Applicant: Corcept Therapeutics Incorporated

Background and Summary

On February 3, 2017, a Safety Labeling Change (SLC) Notification letter was issued to the application holder for this product. The SLC Notification letter required the applicant to revise their prescribing information (PI) and Medication Guide (MG) with updated language following the submission (on April 27, 2016) and review of their final report for study C-1073-36, entitled, “A Phase 1, Open-label, Study in Healthy Subjects to Determine the Effect of 200 mg BID Ketoconazole on the Pharmacokinetics of a Concomitantly Administered 600 mg OD Oral Dose of Korlym® (mifepristone); and of this dose of Korlym on the Pharmacokinetics of Ketoconazole.” This study was conducted to fulfill postmarketing requirement (PMR) 1875-2: a drug-drug interaction clinical trial to determine a quantitative estimate of the change in exposure of mifepristone following co-administration of ketoconazole (a strong CYP3A4 inhibitor), a condition of approval of Korlym on February 17, 2012. The February 3, 2017, letter also notified the applicant that PMR 1875-2 was fulfilled. This letter requested changes to the Dosage and Administration, Drug Interactions, and Clinical Pharmacology sections of the PI, as well as corresponding changes to the MG. See Dr. Sury Sista’s clinical pharmacology review (team leader concurrence by Dr. Jaya Vaidyanathan) dated April 21, 2017, for additional details. Also refer to the following reviews which preceded issuance of this SLC letter:

- November 28, 2016: Clinical Pharmacology review of the final PMR 1875-2 study report by Dr. Sury Sista (team leader concurrence by Dr. Jaya Vaidyanathan).
- January 26, 2017: Office of Prescription Drug Promotion (OPDP) review of currently approved PI and MG (approved with S-006 on October 25, 2016) by Meena Ramachandra. This review included no comments for the PI and noted that they would contribute to the review of the MG that would be filed by the Division of Medical Policy Programs (DMPP).
- January 27, 2017: DMPP review by Sharon Williams (concurrence from team leader Shawna Hutchins and from Meena Ramachandra of OPDP).

The application holder submitted a supplement in response to the SLC Notification letter on March 2, 2017. Comments and revisions were sent by FDA to the applicant on March 23, 2017, and the applicant responded on March 30, 2017. On March 31, 2017, a labeling discussion extension letter was issued. On April 11, 2017, FDA sent revisions and comments to the applicant, and the applicant responded via email on April 14, 2017. Subsequent minor revisions

were made by the applicant on May 15, 2017, and agreed to by FDA on May 16, 2017. The review team reached concurrence on this final PI and MG on May 16, 2017.

Materials Reviewed

This labeling review compared the following labeling for Korlym (mifepristone) tablets:

Labeling Reviewed	Final Proposed Labeling Submission Date	Currently Approved (supplement and date)
Prescribing Information	May 15, 2017 (via email)	NDA 202107/S-006 October 25, 2016
Medication Guide		

Review

The prescribing information and Medication Guide were compared to the currently approved versions, using the Microsoft PDF electronic comparison function. A PDF copy of this comparison document is appended to this review. The changes in the proposed labeling are consistent with the SLC-required changes, as documented in the February 3, 2017, SLC Notification letter and the labeling comments issued on March 23 and April 11, 2017.

Recommendations

The prescribing information and the final proposed Medication Guide submitted on May 15, 2017, were reviewed and found acceptable by Dr. Jennifer Rodriguez Pippins. The supplement is ready for approval.

The final PI should be revised to reflect the addition of “Recent Major Changes” to the Highlights section and corresponding margin marks in the Full Prescribing Information prior to attachment to the approval letter.

Reviewed by: Jennifer Johnson, Regulatory Health Project Manager
(see appended signature page)

Concurrency by: Pamela Lucarelli, Chief, Project Management Staff

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/s/

JENNIFER L JOHNSON
05/16/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202107Orig1s007

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

From: [Johnson, Jennifer](#)
To: ["Sue Rinne"](#)
Bcc: [Johnson, Jennifer](#)
Subject: RE: NDA 202107/S-007 (Korlym): FDA Labeling Comments
Date: Tuesday, April 11, 2017 7:30:56 PM
Attachments: [NDA 202107 Korlym PI FDA edits 11 April 2017.doc](#)

Dear Sue,

Please find attached our latest draft of the Korlym PI, submitted to your NDA 202107/S-007 on March 30th.

We respectfully request a response by close of business on [Monday, April 17th](#).
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 [<mailto:srinne@corcept.com>]
Sent: Thursday, March 30, 2017 7:08 PM
To: Johnson, Jennifer
Subject: RE: NDA 202107/S-007 (Korlym): FDA Labeling Comments

Hi Jennifer,

Thank you so much for the confirmation!

Best regards,
Sue

From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Thursday, March 30, 2017 3:58 PM
To: Sue Rinne
Subject: RE: NDA 202107/S-007 (Korlym): FDA Labeling Comments

Hi Sue,

We did receive the official submission.

Thank you!
Kind Regards,
Jennifer

From: Sue Rinne [<mailto:srinne@corcept.com>]
Sent: Thursday, March 30, 2017 5:34 PM
To: Johnson, Jennifer
Subject: RE: NDA 202107/S-007 (Korlym): FDA Labeling Comments

Hi Jennifer,

Thanks so much for your message.

Best regards,
Sue

From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Thursday, March 30, 2017 2:28 PM
To: Sue Rinne
Subject: RE: NDA 202107/S-007 (Korlym): FDA Labeling Comments

Dear Sue,

Thank you for the update. I'll keep my eyes out for its receipt this evening.
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 [<mailto:srinne@corcept.com>]
Sent: Thursday, March 30, 2017 4:26 PM
To: Johnson, Jennifer
Subject: RE: NDA 202107/S-007 (Korlym): FDA Labeling Comments

Dear Jennifer,

It is nearing the COB (EST) on Thursday, March 30th.
We are submitting the attached response of the proposed labeling via the gateway. It should arrive within the next half hour.

Let me know if you have any questions or concerns.

Best regards,
Sue

Susan Rinne

Vice President, Corporate Regulatory Affairs

Corcept Therapeutics

149 Commonwealth Drive

Menlo Park, CA 94025

Phone 650-688-8784 Fax 650-327-3218 Cell (b) (6)

From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]

Sent: Thursday, March 23, 2017 2:19 PM

To: Sue Rinne

Subject: NDA 202107/S-007 (Korlym): FDA Labeling Comments

Dear Sue,

For S-007 submitted to Korlym NDA 202107 on March 2, 2017, please find attached our comments on your proposed package insert.

Also attached is our rationale in response to your position on labeling changes made to the clinical pharmacology sections.

We kindly request a response by COB next **Thursday, March 30th**.

Let me know if you have any questions or concerns.

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
04/11/2017



NDA 202107/S-007

LABELING DISCUSSION EXTENSION

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

Dear Ms. Rinne:

Please refer to your March 2, 2017, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Korlym (mifepristone) tablets, 300 mg.

On February 3, 2017, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Korlym to address the risk of increased mifepristone exposure when Korlym is administered concomitant with CYP3A inhibitors, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On March 2, 2017, we received your prior approval supplement containing your proposed safety related labeling changes, including changes to the Medication Guide. Section 505(o) requires FDA to promptly review the supplement and, if we disagree with the proposed changes, to initiate discussions with you. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on May 1, 2017.

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

Sincerely,

{See appended electronic signature page}

Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JENNIFER R PIPPINS
03/31/2017

From: [Johnson, Jennifer](#)
To: ["Sue Rinne"](#)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 202107/S-007 (Korlym): FDA Labeling Comments
Date: Thursday, March 23, 2017 5:18:45 PM
Attachments: [NDA 202107_S007_Proposed_PI_clean.doc](#)
[NDA 202107 - PMR label language- FDA Rationale.docx](#)

Dear Sue,

For S-007 submitted to Korlym NDA 202107 on March 2, 2017, please find attached our comments on your proposed package insert.

Also attached is our rationale in response to your position on labeling changes made to the clinical pharmacology sections.

We kindly request a response by COB next **Thursday, March 30th**.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

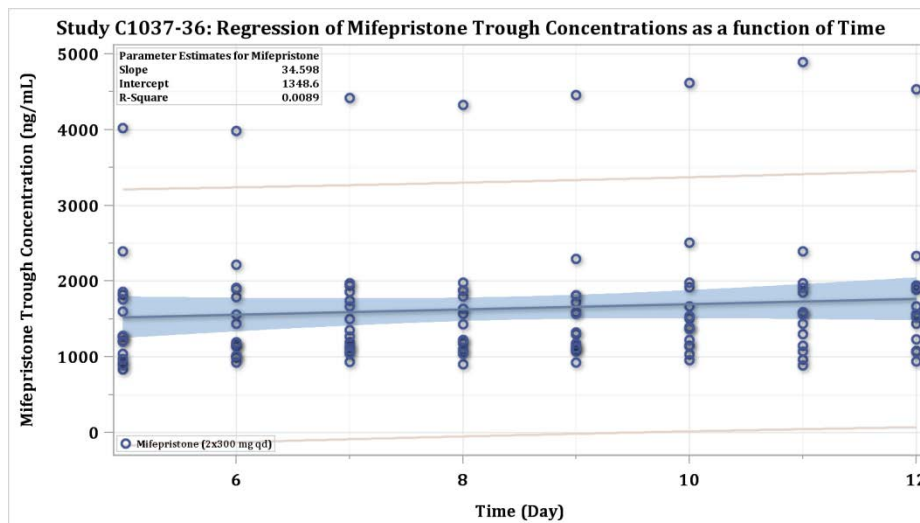
21 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Sponsor's position:

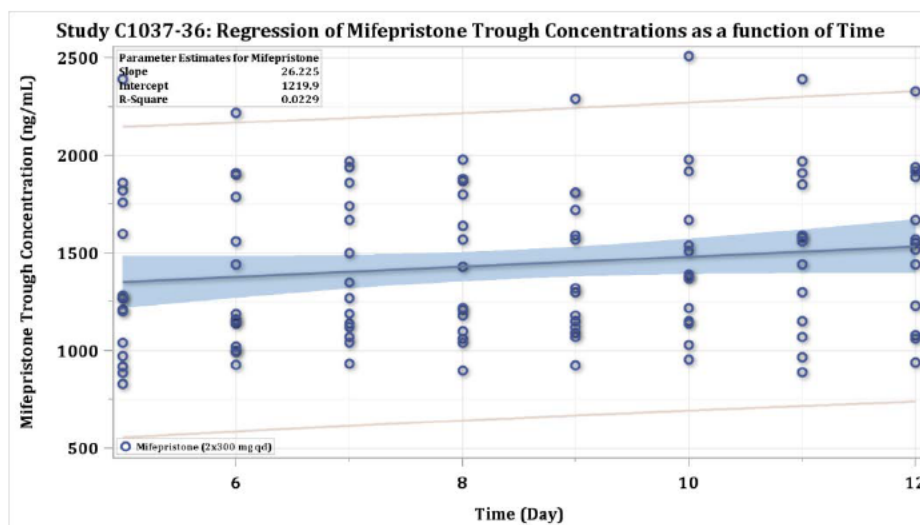
1. The study C1073-36 results may have actually overestimated the effect of CYP3A inhibition since trough concentrations of mifepristone and RU42848 were still increasing day-by-day up to the start of ketoconazole administration on Day 13 (black circles ~~Figure 1~~). This indicates that steady state conditions had not been attained at the time of ketoconazole administration, so that some of the increase in mifepristone exposure from Days 13-17 was likely due to continued accumulation of mifepristone independent of inhibition of CYP3A.

Agency position:

Mifepristone exhibits mechanism-based inhibition of its own metabolism. It is theoretically possible that there is continued accumulation of mifepristone independent of inhibition of CYP3A through days 13-17. However, contrary to the Applicant's position, it appears that steady state was attained by Day 12 (see figure below).



Excluding data from subject (b) (6), who had consistently high concentrations, did not change the outcome.



Sponsor's position:

2. With inhibition of CYP3A, the corresponding increases in C_{max} and AUC_{0-24h} (27.59% and 38.01%, respectively from Table 1) should yield systemic exposures similar in magnitude to those previously attained with 1200 mg daily (i.e., approximately the equivalent of $900 \cdot 1.38 = 1242$). This estimate is imprecise since 1.) across multiple pharmacokinetic studies with mifepristone, increases in C_{max} and AUC_{0-24h} are smaller than dose-proportional (Korlym NDA 202107 Module 2.7.2, Table 45), and 2.) the pharmacokinetic studies did not examine the dose-proportionality of daily doses of 900 and 1200 mg. (b) (4)

The other key result from study C1073-36 was that CYP3A inhibition increases exposure to one of the three metabolites (RU 42698) to a larger magnitude than for mifepristone: 69% for C_{max} and 67% for AUC_{0-24h} . Both values are mid-way through the range of "weak" inhibition. Figure 1 shows that steady state conditions were attained for this metabolite prior to ketoconazole administration; therefore, the point estimates can be considered reliable. However, this metabolite is less potent than mifepristone at the glucocorticoid receptor (Table 2). As a result, this modest increase in exposure is likely less important compared to the even smaller increase in exposure to mifepristone.

However, the point estimate of 87% for GMR of the AUCs suggests exposure from 600 mg is on the low side, (b) (4)

. Regardless, based on these calculations, the current 300-mg cap on daily dosing in subjects who require co-administration of a strong CYP3A inhibitor could compromise the clinical response in patients who previously benefitted from larger doses of Korlym.

Agency position:

In the absence of dose-proportionality, extrapolation of systemic exposures by multiplying a theoretical dose with the factor increase seen at a lower dose is unacceptable. Similar extrapolation of cross-study data shown in Sponsor's Table 3 would yield a test/reference geometric mean ratio of 130.91% for mifepristone AUC_{0-24h} at a dose of 900 mg ($87.27 \cdot (900/600)$), indicating a mean 31%

increase (upper bound of 47.3%)in systemic exposure over than that observed at the 1200 mg dose. This is in contrast to the 15% less exposure with the 600 mg dose compared to 1200 mg.

Following multiple dosing, the exposure of RU42633 is 1.28 folds compared to the parent, Mifepristone

(http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202107Orig1s000ClinPharmR.pdf).

With a potency of 0.61 compared to the parent, and a 1.02 fold increase in exposure in presence of Ketoconazole, the total potency contribution of RU42633 would be 0.80 ($1.28 \times 0.61 \times 1.02$). Similarly the total potency contributions of RU42698 and RU42848 would be 0.38 and 0.36, respectively. As can be seen, the total potency of the metabolites when added together would exceed that of mifepristone.

Sponsor's position:

3. *In summary, data from study C1073-36 show that mifepristone is an insensitive substrate for CYP3A, such that the effect of ketoconazole on mifepristone corresponds to what FDA defines as "weak" inhibition.* (b) (4)

Agency position:

From the data shown in Table 3, the exposure following 600 mg mifepristone was in the range of the exposure seen with 1200 mg mifepristone. The impact of potential exposures in excess (b) (4) when co-administered with a strong CYP3A4 inhibitor is not known.

Based on the findings from this study, the Agency agrees to remove language regarding moderate CYP3A inhibitors from the product label. (b) (4)

. The dose of KORLYM should be limited to 600 mg, and strong inhibitors of CYP3A should be used only when necessary.

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/s/

JENNIFER L JOHNSON
03/23/2017