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RESEARCH**

APPLICATION NUMBER:
202107Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 17, 2012
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA #	202107
Supplement #	(cross reference IND 76480)
Applicant Name	Corcept Therapeutics, Inc.
Date of Submission	April 18, 2011
PDUFA Goal Date	February 17, 2012
Proprietary Name / Established (USAN) Name	Korlym (mifepristone immediate-release tablet)
Dosage Forms / Strength	300-mg tablets
Proposed Indication(s)	To control hyperglycemia in adult patients with endogenous Cushing's syndrome with T2DM or glucose intolerance who have failed surgery or are not candidates for surgery
Action/Recommended Action for NME:	Approval

1. Introduction

Corcept Therapeutics has submitted this new drug application (NDA) under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FDCA) for the use of Korlym® (mifepristone) in the treatment of patients with endogenous Cushing's syndrome who have failed surgery or are not candidates for surgery.

Cushing's syndrome is due to hypercortisolism and its clinical and metabolic consequences. It is broadly separated into exogenous and endogenous forms, the former due to exogenous glucocorticoid administration for varied medical conditions and the latter due to the body's over production of cortisol. Endogenous Cushing's syndrome is further divided into ACTH-dependent and ACTH-independent forms to distinguish between an extra-adrenal or intra-adrenal pathology.¹ As this application is only for the treatment of endogenous Cushing's syndrome, the remainder of this memo will refer to Cushing's syndrome with an understanding that it is specific to only the endogenous forms of this condition.

Approximately 80-85% of Cushing's syndrome are ACTH-dependent with 80% of these due to a pituitary tumor (Cushing's disease) and 20% due to ectopic ACTH secretion from a non-pituitary tumor with the most prevalent ones being bronchial carcinoid and small cell lung

¹ Pivonello R et al. Cushing's Syndrome. *Endocrinology and Metabolism Clinics of North America*. 2008; 37(1): 135-149.

cancer although any tumor of neuroendocrine origin may produce ACTH.² Of the approximate 15-20% of ACTH-independent Cushing's syndrome, the majority are due to an adrenal tumor. Cushing's syndrome is a rare disease with an incidence of 0.7 to 2.4 per million population per year. This application received orphan designation on July 5, 2007.

The diagnosis of Cushing's syndrome requires a multitude of laboratory and radiologic tests whose discussion extends beyond the scope of this memo. The objective of the laboratory tests is to demonstrate inappropriate and sustained hypercortisolism to distinguish these patients from conditions such as pseudo-Cushings, severe depression, or cyclical Cushing's. Reliance on just clinical presentations is not possible or acceptable as patients' presentations are highly variable and span a wide spectrum that includes textbook descriptions of buffalo hump, violaceous striae, hirsutism and facial plethora to more subtle signs of just diabetes and depression. The etiology of the syndrome may also influence the clinical presentation. For example, the age range of patients with ectopic ACTH syndromes is generally a decade older than those with Cushing's disease with a lower female to male ratio. Patients with ectopic ACTH syndrome or adrenal cancers may also present with more severe signs and symptoms of hypercortisolism, and due to the underlying malignant nature of the tumor, these patients often have greater morbidity.

Regardless of the etiology of Cushing's syndrome, the treatment goal is the same and in all cases, if the underlying tumor can be located, surgical resection is the preferred initial therapy. Medical therapy may be initiated prior to surgery to control the hypermetabolic state and is often relied upon afterwards if surgery is unsuccessful or the tumor recurs. In some patients, radiation therapy and/or bilateral adrenalectomy are considered. The available medical therapies are limited and unapproved for Cushing's syndrome.³ Their use has been based on the knowledge of their effects at inhibiting certain enzymes in the adrenal steroidogenesis pathway (e.g., ketoconazole or metyrapone) or limited inhibition of ACTH (e.g., somatostatin). Mifepristone employs a different strategy in treating Cushing's syndrome: blockade of the glucocorticoid II receptor (GR) to inhibit the actions downstream from this receptor. It also blocks the progesterone and androgen receptor, the former activity being the basis for its use in termination of pregnancy.

2. Background

There were two main challenges in the review of this application. The first was a scientific matter and the second was a regulatory/legal one.

On the scientific note, the trial design to establish safety and effectiveness of Korlym for this indication was limited by 1) the underlying medical condition and 2) the pharmacologic action of the drug. Given the rarity and progressive nature of the condition with limited medical options, the type of trial design would have to be an uncontrolled and open-label design in a limited number of patients. Such a trial design in a small sample of patients complicates

² Alexandraki K and Grossman A. The ectopic ACTH syndrome. *Rev Endocr Metab Disord.* 2010; 11: 117-126.

³ Mitotane is an exception but it has a limited indication in only patients with adrenal carcinomas

attribution of effect and safety to drug. The mechanism of action of the drug presented another complexity as to the appropriate endpoint to evaluate effectiveness of Korlym. Just as the diagnosis of Cushing's syndrome requires evidence of elevated cortisol levels, the treatment of these patients relies on a demonstration of reduced cortisol levels as a measure of response and/or success. Since the drug's selective antagonism of the GR does not result in reduced cortisol levels, this biomarker was not of any utility for establishing efficacy and could not be employed as a measure for dose titration. Sections 6.0 and 7.0 of my memo delve further into the trial design and how the reviewers considered multiple lines of evidence to make a determination of safety and effectiveness.

The regulatory and legal challenge of this application is because of the more controversial use of this active ingredient for medical termination of pregnancy in the approved formulation, Mifeprex®. Given as one-time lower doses than proposed in Cushing's syndrome, mifepristone binds to the progesterone receptor (PR) to achieve pregnancy termination. Mifeprex, manufactured by Danco, was approved on September 28, 2000 under 21 CFR Subpart H and is available only through a restricted distribution program. With passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) was applied to Mifeprex on June 8, 2011. Mifeprex is not distributed to or dispensed through retail pharmacies but is limited to specialty clinics and prescribed by physicians who have enrolled in a certification program. (Please see DRISK review for a full description of the Mifeprex REMS with ETASU).

Prior to the submission of Korlym and throughout the NDA review, multiple internal meetings and discussions were held to determine if Korlym and its proposed indication met the regulatory requirements for a REMS with ETASU or if one would be necessary to maintain the integrity of Mifeprex's REMS with ETASU.

Dr. Dragos Roman in his cross-discipline team leader (CDTL) memo has clearly outlined these discussions and the reader is also referred to memos written by DRISK reviewers, Drs. Robotom, LaCivita, and Karwoski, and meeting minutes prepared by Dr. Amy Egan for a meeting involving CDER Center Director and senior managers in OND, OSE, and ORP. On November 3, 2011, a CDER recommendation was made that given the rarity and seriousness of Cushing's syndrome and the unique situation in which it would be used, a REMS with ETASU was not warranted. However, the applicant has agreed to establish a voluntary limited distribution system and a drug utilization study will be required postmarketing. Please see Section 13.0 for further discussions of the PMR for this application.

3. CMC/Device

CMC has recommended approval without any additional testing or studies required. Please see reviews of Drs. Ysern and Al-Hakim dated January 12, 2012.

4. Nonclinical Pharmacology/Toxicology

The applicant conducted several nonclinical studies to support the chronic use of mifepristone. These included safety pharmacology studies to evaluate potential of mifepristone to inhibit Ki channels, pharmacokinetic/ADME/and toxicokinetic studies, repeat-dose toxicity studies, in vitro genetic toxicology studies, and carcinogenicity studies. Published literature and studies conducted under approved NDA 20687 for use of mifepristone in pregnancy termination were also relied upon by the applicant as permitted under 505(b)(2). The three major metabolites of RU486 identified in humans were also present in mice, rats, dogs, and monkeys and were therefore adequately evaluated in the nonclinical program.

Please see Dr. Patricia Brundage's review dated January 19, 2012, for details of the nonclinical program supporting approval of this NDA. She and pharmacology/toxicology supervisor, Dr. Todd Bourcier, deem data acceptable in support of approval of mifepristone for Cushing's syndrome provided labeling accurately reflects the nonclinical findings and their recommendations on use of the product. Dr. Bourcier's memo dated February 7, 2012, also outlines the sufficient bridging data to Mifeprex® supporting reliance on FDA's finding of safety and effectiveness for some aspects of this application. No postmarketing trials are being proposed by this discipline.

Several of the safety findings identified reflect the pharmacology of mifepristone as an anti-glucocorticoid and anti-progesterogenic drug. The first of these effects is the basis for evaluating the use of mifepristone in the treatment of Cushing's syndrome. Antagonism at the progesterone receptor is also included in the label and discussed in other sections of this memo with regard to the effect on fertility and pregnancy.

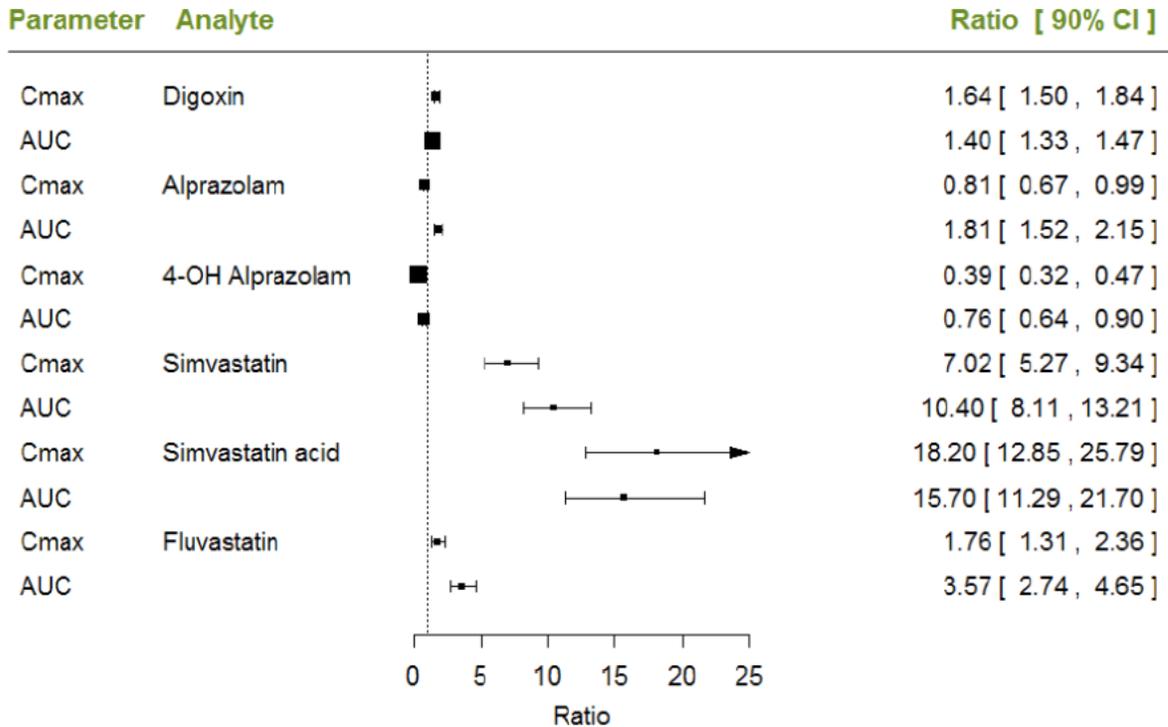
Two hERG channel studies were performed of which one showed a concentration-related inhibition of potassium selective IKr current with mifepristone and its metabolites. A 12-month toxicity study in dogs also revealed a slight QTc prolongation in higher-dosed animals. These findings alongside the clinical tQT study support information on the potential QT prolongation effect of mifepristone in labeling with caution to be applied when used with drugs which might increase mifepristone drug exposures.

5. Clinical Pharmacology/Biopharmaceutics

Please see review of Drs. Jee Eun Lee and Jayabharathi Vaidyanathn dated January 13, 2012. Thirteen clinical pharmacology studies have been conducted by applicant and submitted to this NDA.

Drug-drug interaction studies (DDI) were conducted with digoxin (P-gp substrate), alprazolam and simvastatin (CYP3A substrate), fluvastatin (insensitive CYP2C8/9 substrate), and cimetidine (mild CYP3A inhibitor). No DDI studies were conducted to address the effect of strong CYP3A4 inhibitors. The results from these studies are illustrated in the following figure:

Effects of Mifepristone on Other Drugs



*Simvastatin dose in multiple dosing regimen is 80 mg while 40 mg in single dosing regimen (Exposure was not normalized by dose)

Figure 10. Forest plot for DDI with mifepristone

Given the significant increase in sensitive CYP3A substrate simvastatin, contraindications are proposed for simvastatin and lovastatin plus other CYP3A4 substrate drugs with narrow therapeutic indices.

The applicant was asked to conduct a DDI with a potent CYP3A4 inhibitor. This was not done and the applicant instead provided 2 randomly-timed concentrations of mifepristone from one patient who was on concomitant ketoconazole therapy during his participation in Study 400. This was not deemed acceptable. (b) (4)

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After further discussion it was decided that potential DDI with potent CYP3A4 inhibitors would be more appropriately discussed in Warnings and Precautions recommending against their use with mifepristone unless medically necessary. In addition the label will recommend limiting the dose of mifepristone to 300 mg daily if a strong CYP3A4 inhibitor must be used concomitantly. A DDI study with ketoconazole will be required. Depending on the results of this study, updates to labeling may occur.

Thorough QT Study

A tQT study was conducted; please see the IRT review dated October 20, 2011. This study was a 14-day, multiple-dose, parallel treatment design enrolling 180 healthy male subjects but due to adverse events resulting in high discontinuation rates, data are limited out to Day 14. Mifepristone doses of 600 and 1800 mg were employed, the latter providing suprathreshold exposures. A single oral dose of moxifloxacin 400 mg was used as a positive control.

Overall, the study results were inconclusive because assay sensitivity was not established. The largest lower bound of the 2-sided 90% CI for the pbo-adjusted, baseline-corrected QTcI for moxifloxacin was < 5 ms; therefore, small changes in QTc interval cannot be excluded. Despite this shortcoming, the largest upper bounds of the 2-sided 90% CI for the mean difference between mifepristone 1800 mg and placebo did exceed 10 ms at several time points. No such finding was observed in the 600 mg dose group. This finding along with the one positive hERG channel study suggests a potential for QT prolongation associated with mifepristone use with increasing exposures.

The proposed label will note that mifepristone and its metabolites block IKr, based on nonclinical data, and that Korlym prolongs QTc interval in a dose-related manner. More cautionary language is proposed with regard to using lowest effective dose. Since a DDI study has not been conducted with a potent CYP3A4 inhibitor, we will recommend limiting dose of Korlym to 300 mg if combined use with a potent inhibitor is necessary. The applicant will be required to conduct this DDI study with ketoconazole. Depending on the results, labeling may be revised accordingly.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Limitations of Clinical Development Program to be Considered

One pivotal efficacy and safety trial was conducted by the applicant in support of this NDA. Published studies of mifepristone in Cushing's syndrome were also submitted and summarized in Dr. Zemskova's review but none of these studies was relied upon for the demonstration of efficacy of Korlym and are therefore not discussed in this memo.

C1073-400 or Study 400 was a 24-week, open-label, uncontrolled trial that enrolled a total of 50 patients with endogenous Cushing's Syndrome. The stated objectives of the trial were to evaluate the safety and efficacy of mifepristone in the treatment of the signs and symptoms of endogenous Cushing's syndrome. These are very broad objectives and in reality, only two endpoints were identified and patients were selected specifically to evaluate these endpoints: glycemic control and blood pressure.

Before presenting the trial results, a discussion on several aspects of the trial design, endpoints, and patient population, and how they impact data interpretability will be necessary.

Trial Design (Open-label and Uncontrolled)

The open-label and uncontrolled nature of a trial can introduce confounders, biases, and limitations that are often mitigated through the conduct of a randomized, double-blind, and controlled trial. For this condition, a placebo control arm could not be employed because the progressive and serious nature of the condition would make it unethical to randomize any patient to placebo.

An active-controlled trial to currently available therapies was not considered for several reasons. With exception for mitotane, which is approved for the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types, all medical therapies employed in practice for the treatment of Cushing's syndrome are used off-label. The treatment regimens and efficacy of these other medical therapies have not been adequately assessed beyond case reports and anecdotal experience. In addition, these other drugs target a reduction in cortisol levels which cannot be achieved with Korlym by virtue of mifepristone's mechanism of action. Selecting an appropriate and easily quantifiable endpoint that can compare the effects of the off-label therapies and Korlym could not be identified for a well-designed, active-controlled trial. Similarly, radiotherapy, which is also a treatment option in Cushing's syndrome, would not be an appropriate active control given its variable success rate and time to demonstration of efficacy measured over the course of years.

Untreated hypercortisolism in Cushing's syndrome is progressive with little to no expectation of spontaneous improvement (e.g. the very rare instance of pituitary apoplexy in Cushing's disease). For this reason, an uncontrolled trial of Korlym that could assess a clinically relevant efficacy endpoint might produce results which can be reasonably attributed to the drug. However, this limitation of the trial design must still be considered in the evaluation and conclusions made of the study results.

Efficacy Endpoints

As stated in the Introduction and Background sections of this memo, the mechanism of action of Korlym is antagonism of the GR preventing the downstream effects of cortisol on its receptor. Unlike other interventions targeting a reduction in cortisol levels, Korlym does not reduce serum cortisol and in some cases cortisol levels may increase. Furthermore, despite biochemical hypercortisolism, patients can become adrenally insufficient as a result of absent post-receptor activation.

During the IND stage, FDA agreed with the applicant that demonstration of an effect on some other biochemical parameter will be accepted. The original protocol submission included very broad assessments of a composite clinical endpoint which was ultimately modified (with FDA input) to a demonstration on improvements in glycemic control and/or blood pressure defined as:

1. The change in the area under the concentration-time curve for glucose (AUC_{glu}) in the 2-hr oral glucose tolerance test (oGTT) from baseline to Week 24
2. A change from baseline to Week 24 in mean diastolic blood pressure (DBP)

Secondary endpoints included a blinded assessment of selected signs and symptoms of Cushing's syndrome as well as laboratory findings by a Data Review Board, body weight, use of concomitant medications for diabetes and hypertension, levels of HbA1c, systolic blood pressure, and photographs. There were exploratory efficacy variables assessed which will not be discussed in this memo. It should be noted that no hierarchical sequence for analysis was applied in the analysis of secondary endpoints. Although FDA did not object to this, FDA did note that control of Type 1 error for secondary endpoints would be important for consideration of labeling.

The trial selected patients but did not randomize them into subgroups which would be evaluated specifically for one of the two primary endpoints. These subgroups are referred to as the Diabetes Mellitus (DM) and the Hypertension (HTN) cohorts.

FDA has well-established efficacy criteria for therapies intended for the treatment of hyperglycemia in diabetes mellitus. The primary efficacy endpoint in both T1 and T2DM trials has been HbA1c which is a reliable measure of glycemic control and a surrogate for clinical benefits (e.g., microvascular complications). HbA1c was not selected as a primary efficacy endpoint in the Cushing Syndrome population because the clinical presentation of diabetes is variable in this condition and adjustments in anti-diabetic therapies are expected which would hinder the interpretation of results, especially in an uncontrolled study. As the DM cohort also included a few patients with glucose intolerance, a change in HbA1c from baseline might not be as reliable of a measure in these patients as they would have normal values at baseline. Reliance on a change in AUC_{glu} during a 2-hr oGTT is a reasonable alternative assessment of glycemic response as it is under a controlled setting (unlike self-blood-glucose monitoring); is administered via a protocol; and is an objective laboratory measure. Nonetheless, results can be influenced by certain patient behaviors. Furthermore, unlike HbA1c, the clinical relevance of a reduction in AUC_{glu} during an oGTT is unknown. Hence, the effect of Korlym on glycemic control will focus on both this primary efficacy measure supported by changes in HbA1c and anti-diabetic medications.

Anti-hypertensive therapies have been approved based on mean changes in systolic and/or diastolic blood pressure. Hence, the endpoint of change in DBP is not unprecedented for drug approval. However, the effect of Korlym on blood pressure proved to be more difficult to demonstrate than anticipated and the results were obfuscated by the inclusion criteria, protocol violations, and use of certain anti-hypertensive medications. In retrospect, establishing efficacy of Korlym in Cushing's syndrome based on blood pressure reduction should not have

been considered a primary endpoint because the increased cortisol levels resulting from the drug's mechanism of action may actually exacerbate hypertension secondary to mineralocorticoid receptor activation. Nonetheless, this memo will highlight these results from both an efficacy and safety perspective.

Patient Population

Given the rarity of this condition, the sample size in the pivotal trial was only 50 which is a limitation for evaluating efficacy and safety for chronic use but not unexpected for orphan indications. FDA has approved other therapies for rare disease with similar sample sizes (NDA for Increlex included 71 pediatric patients with severe Primary IGF-1 deficiency).

It should be noted that despite the limited patient numbers in the pivotal trial, other clinical data of mifepristone in Cushing's patients from published literature served as supportive evidence for efficacy and informed us in the design of the Phase 3 trial. None of these studies, which are summarized under Section 6.1.10, 7.7.2, and 9.1 of Dr. Zemskova's review, will be included in labeling.

Efficacy in Diabetes (DM) Cohort

There were 29 out of 50 patients enrolled in Study 400 who were evaluated under the DM Cohort. Twenty-four (83%) had Cushing's disease; 3 had ectopic ACTH and 2 had adrenal carcinoma. Twelve of the 24 patients with Cushing's disease had prior radiation therapy whose data were reviewed separately by Dr. Zemskova to determine whether this previous treatment could account for any observed efficacy associated with Korlym. In her review, she pointed out that ACTH levels remained elevated in these patients despite radiation therapy. This would be evidence that radiation therapy was not successful and unlikely contributory to any efficacy observed in Study 400.

Patients in this cohort underwent a 75-g oGTT at screening, on Day 1, Wks 6, 10, 16, and 24 or on early termination visits. A patient was considered a responder if he/she had a 25% or more decrease in AUCglu at Wk 24 or early termination visit from baseline. A statistically significant reduction in AUCglu was defined by a responder analysis in which the lower bound of the 95% CI of this response rate had to exceed 20%. Approximately 60% of patients were responders and the lower bound of the 95% CI was 42%. From the cumulative distribution function curve provided by the applicant it is evident that the majority of patients had a reduction in AUCglu from baseline. The following table from Dr. Zemskova's review summarizes the individual response for the 24 patients included in this analysis.

Table 19. Cumulative Distribution Function for Percent Reduction in AUC_{glucose} at Week 24/ET in C-DM Subjects (mITT population)

% Reduction from Baseline	Cumulative Distribution of Change, n (%)	Improved/ Worsened
-68.7	1 (4.17)	Improved
-60.6	2 (8.33)	Improved
-50.7	3 (12.50)	Improved
-48.2	4 (16.67)	Improved
-47.0	5 (20.83)	Improved
-46.5	6 (25.00)	Improved
-45.3	7 (29.17)	Improved
-43.9	8 (33.33)	Improved
-42.4	9 (37.50)	Improved
-41.2	10 (41.67)	Improved
-37.1	11 (45.83)	Improved
-36.9	12 (50.00)	Improved
-35.3	13 (54.17)	Improved
-28.0	14 (58.33)	Improved
-25.0	15 (62.50)	Improved
-24.2	16 (66.67)	Improved
-19.8	17 (70.83)	Improved
-4.4	18 (75.00)	Improved
-3.8	19 (79.17)	Improved
-3.5	20 (83.33)	Improved
-0.8	21 (87.50)	Improved
4.7	22 (91.67)	Worsened
26.5	23 (95.83)	Worsened
33.2	24 [^] (100.00)	Worsened

Source: Sponsor’s table 15, Module 5, Vol 31, p. 73;

[^]One subject was excluded from mITT analysis (#20-022), because he did not have AUC_{glucose} values post-baseline.

In those patients who responded to treatment, a reduction in AUC_{glu} was observed by Week 6 in most patients and was sustained for the duration of treatment out to Week 24 (see Figure 3 in Dr. Zemskova’s review).

As stated above, AUC_{glu} is not a standard efficacy endpoint for anti-diabetic medications and was accepted only for the unusual circumstances of evaluating glycemic control in Cushing’s patients treated with Korlym. However, the applicant also provided data on HbA1c reduction in 21 patients who had baseline and post-baseline values. The mean reduction from baseline in these patients was 1.14% (2-sided 95% CI: -1.56, -0.65; p=0.0001). This magnitude of reduction has been observed in currently approved anti-diabetic applications and considered to be clinically relevant. Dr. Zemskova further evaluated those patients with HbA1c levels above normal at baseline (6.5% - recall that trial enrolled patients with glucose intolerance or could have enrolled a diabetic patient with adequate control). In 14 patients with elevated HbA1c levels at baseline, all had a reduction from baseline including some with robust reductions of 2 to 4% accompanied by reductions in anti-diabetic medications or doses.

In conclusion, while this trial employed an untraditional measure of glycemic control and was uncontrolled, a correlation of AUC_{glu} to clinically meaningful endpoints such as HbA1c reduction and dose reduction of antidiabetic medications could be established including several very robust effects (e.g., reduction from 10.4 to 6.0% in HbA1c level in one patient or

~ 50% reduction in insulin requirements). These data constituted substantial evidence that Korlym would treat hyperglycemia associated with diabetes or glucose intolerance in Cushing's syndrome. However, the observed effects should not be extrapolated beyond this patient population and it would be inappropriate to consider the use of Korlym in the management of diabetes unrelated to hypercortisolism due to Cushing's syndrome. Labeling should indicate this as a Limitation of Use.

Efficacy in Hypertension (HTN) Cohort

Unlike the effect observed in the DM-cohort, the response rate in the HTN cohort was equivocal. Drs. Zemskova and Roman discuss some of the design flaws which might have contributed to the difficulty in establishing a robust effect and I will not reiterate them here. I believe that some aspect of the results reflect the pharmacologic effect of mifepristone. Hypertension in Cushing's syndrome is partly due to high circulating levels of cortisol which can bind to the mineralocorticoid receptor. Acting like aldosterone, patients can present with hypokalemia and hypertension. Since mifepristone blocks the glucocorticoid receptor but does not cause a reduction in circulating cortisol levels, these patients are still prone to mineralocorticoid effects of hypercortisolism.

Effects on Clinical Signs and Symptoms of Cushing's Syndrome in Overall Cohort

It should be noted that no plan was submitted to FDA for review by the Study Endpoints and Labeling of Drugs (SEALD) review team with respect to patient reported outcome measures. FDA reviewers have determined that while these endpoints should be evaluated in a clinical trial, the limitations of the assessments in an open-label, uncontrolled trial should preclude any quantitative statements in labeling.

A Data Review Board (DRB) comprised of 3 experts on Cushing's syndrome performed a review of 8 categories of clinical parameters to evaluate whether a patient's signs and symptoms of Cushing's had changed. These categories included:

1. assessment of glucose homeostasis
2. assessment of blood pressure
3. assessment of lipids
4. changes in weight and body composition
5. clinical scoring and appearance (e.g., acne, hirsutism (in women only), Cushingoid appearance)
6. strength assessments
7. psychiatric and quality of life assessments
8. metabolic bone assessments

The DRB reviewed adverse events, concomitant medication data, and all efficacy assessments obtained at baseline, Weeks 6, 10, 16 and 24 or end of treatment, and at the follow-up visit. Baseline and follow-up evaluations were identified, but data from other visits were reviewed in a blinded fashion with respect to visit. The DRB did not know the dose of drug or the sequence in which the visit occurred. It should be noted that while the DRB reviewers are blinded to the sequence of visits, some of the assessments at each visit were evaluated by a

clinical investigator who was NOT blinded. After reviewing the data, each DRB member assigned an overall score for each visit as follows:

- 1: worse than baseline
- 0: unchanged from baseline
- +1: clinically significant improvement

The median of the 3 scores was calculated and a score of +1 was considered evidence of clinical improvement. A responder was defined as a subject whose median score was +1 at any visit after the baseline visit. Based on the applicant's definition of responders, they report that 87% of patients (40/46) in the mITT population had a clinical improvement at any point in time and deemed the findings statistically significant based on a calculated 95% CI yielding a lower bound of > 30%, an arbitrary cut point considered by applicant as adequate to account for variability in response.

Drs. Zemskova and Choudury appropriately point out the limitations of this endpoint assessment. The open-label nature of the trial is always problematic in evaluating subjective measures such as quality of life where patient reports may be perceptions based on expectations of clinical improvements or side effects based on knowledge that he/she is receiving an investigational agent. This is further compounded by the absence of a control group for comparison of response for the less subjective measures. In addition, declaring a patient as a responder at any visit also allows the applicant many opportunities for concluding success on this endpoint.

Finally, it is not clear how the reviewers ranked the clinical relevance of the 8 clinical parameters in their scoring. The form for this scoring is provided below.



Corcept Therapeutics

Data Review Board Evaluation

Study: C1073-400

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BLINDED REVIEW RESULTS				
Subject ID: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>				
REVIEWER NAME: _____ <i>Printed Name</i>				
Scoring:				
-1 = Worse than Baseline				
0 = Unchanged from Baseline				
+1 = Clinically significant improvement from Baseline				
VISIT	RESULT			
	<i>(Please check one (and only one) box per visit)</i>			
VISIT A	<input type="checkbox"/> -1	<input type="checkbox"/> 0	<input type="checkbox"/> +1	<input type="checkbox"/> N/A- No data
VISIT B	<input type="checkbox"/> -1	<input type="checkbox"/> 0	<input type="checkbox"/> +1	<input type="checkbox"/> N/A- No data
VISIT C	<input type="checkbox"/> -1	<input type="checkbox"/> 0	<input type="checkbox"/> +1	<input type="checkbox"/> N/A- No data
VISIT D	<input type="checkbox"/> -1	<input type="checkbox"/> 0	<input type="checkbox"/> +1	<input type="checkbox"/> N/A- No data

Reviewer Signature:	<input style="width: 100%;" type="text"/>
Review Date:	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <i>day month year</i>

There is no breakdown of how response in categories such as blood pressure or metabolic parameters might have contributed to the scores or if there was worsening in one and improvement in another, how these components were weighted in the overall score of -1, 0 or 1. To add further to the subjectivity of this assessment, it is not clear how some of these parameters which had their own scoring system were translated to the -1, 0, or 1 categories. For example, acne was rated using a Global Acne Scoring System (CAGS) by the clinical investigator not the DRB reviewer which is described under Section 18.3.3.1 of the applicant’s Clinical Study Report. Different locations of the body are assessed and given a Grade of 0-4 which contributed to a Local Score. The sum of the Local Scores is called the Global Score for acne and can be: 0 None; 1-18 Mild; 19-30 Moderate; 31-38 Moderately Severe; or > 39 Severe. Did a Global Score of 40 on one visit and 38 on another get rated as 0 or +1 by the blinded DRB reviewer?

Despite the inability to rely on these assessments, review of patient narratives does point to individual responses on some endpoints. Care for these patients by several on the FDA review team has given us an appreciation that for many of these patients who have limited options, some of these clinical responses are meaningful, even if other signs or symptoms show worsening. While the label will not state that Korlym is indicated for improving clinical signs and symptoms of Cushing's syndrome, a statement under the Clinical Studies section describing the variable responses to treatment, including some patients reporting improvement, was considered appropriate by the review team provided that no statistical significance be applied to any of these findings.

8. Safety

In contrast to the review of efficacy which relied on one trial, safety of Korlym was based on Study 400, its ongoing extension (Study 415), and several Phase 1, 2 and 3 studies, including studies conducted by the applicant using Korlym for the treatment of other medical conditions. For purposes of labeling, only some of these studies were relied upon. Please see Dr. Zemskova's review for a thorough assessment of safety based on all studies submitted or referenced. Given the variable patient population and study designs, safety data across studies were not pooled.

Just as it was the case in evaluating efficacy, the absence of a control group in Study 400 and 415 is a limitation in assessing a causal relation to drug treatment in the assessment of safety. Furthermore, the co-morbidities associated with Cushing's syndrome often result in serious complications. This is evident in Dr. Zemskova's review of several nonfatal serious adverse events in which she ascribed certain events to drug or as being exacerbated by drug only after careful consideration of the clinical presentation. Despite the lack of a control group, adverse events related to the mechanism of action of mifepristone should be anticipated. Please see section 7.3.5 of Dr. Zemskova's review and Dr. Roman's CDTL memo for a discussion of events of adrenal insufficiency, endometrial hyperplasia/vaginal bleeding and mineralocorticoid excess resulting in severe hypokalemia. Specific sections under Contraindications and Warnings and Precautions will convey these safety concerns.

There were 5 deaths in Studies 400 and 415: four occurred during Study 400 and one during Study 415. The narratives for these deaths are summarized in Section 7.3 of Dr. Zemskova's review who considered the deaths related to progression of disease. Three patients who died in Study 400 had metastatic adrenal carcinoma and the 4th patient had ectopic ACTH-secreting neuroendocrine carcinoma with metastases. The 5th patient in Study 415 had Cushing's disease. The patient was noted to have markedly elevated alkaline phosphatase and bilirubin at the onset of Study 415. Further work-up included a liver biopsy revealing amyloidosis, and a bone marrow aspirate revealing multiple myeloma. The patient's condition deteriorated rapidly thereafter with development of renal failure, hypotension and disseminated intravascular coagulation prior to death.

As noted in the Introduction, mifepristone's antagonism of the progesterone receptor is used in combination with misoprostol for medical termination of pregnancy. The higher doses of mifepristone used in the treatment of Cushing's syndrome are expected to have a similar effect in a pregnant woman. However, differences in this patient population lend themselves to a lower likelihood of unplanned pregnancy and termination. The hypercortisolemic state often renders a patient amenorrheic from secondary hypogonadism. Furthermore, the high doses of mifepristone used for glucocorticoid antagonism is also a contraceptive. Nevertheless, all female patients had to have negative pregnancy screening prior to initiation of therapy and women of childbearing potential had to use an acceptable non-hormonal form of contraception with regular counseling against becoming pregnant. No pregnancies were reported in this program.

Other safety concerns which will be discussed in labeling include immunosuppression, increased TSH levels and rash. Of note, immunosuppression should be discussed with the following in mind:

Immunosuppression – predisposition to infections

Patients with Cushing's syndrome are immunocompromised due to the hypercortisolemic state. In addition, these patients have other co-morbidities (e.g., diabetes) which increase the risk of infections in this patient population. Several infections were reported by Dr. Zemskova but one should be discussed only as it has been reported in the literature as related to the effective control of hypercortisolemia.

A 41 yo male with ectopic Cushing's syndrome secondary to metastatic thymic carcinoid was diagnosed with pneumonia about one month after initiation of Korlym. The patient was treated for presumed *Pneumocystis jirovecii* (formerly *carinii*). This case is described on page 118 of the clinical review.

Pneumocystis jirovecii is known to occur in severely immunocompromised patients and several reports of this form of pneumonia occurring in Cushing's syndrome have been reported in published literature.^{4,5,6} In some reports, the pneumonia was diagnosed shortly after treatment for Cushing's was initiated. The authors of these reports suspect a subclinical picture of pneumocystis in patients with Cushing's syndrome due to their immunocompromised state which is kept at bay by high circulating cortisol levels. With a reduction in cortisol levels or a blockade of cortisol activity, this suppression of an acute immune response to the infection is disrupted resulting in severe pulmonary distress and compromise. Supporting this notion is the recognition in the 1990s that addition of high dose glucocorticoids to antibiotic treatment of pneumocystis in AIDS patients resulted in improved clinical outcomes.

⁴ Arlt A et al. Fatal pneumocystis jirovecii pneumonia in a case of ectopic cushing's syndrome due to neuroendocrine carcinoma of the kidney. *Exp Clin Endocrinol Diabetes*. 2008 Oct; 116(9):515-9.

⁵ Oosterhuis JK et al. Life-threatening pneumocystis jiroveci pneumonia following treatment of severe Cushing's syndrome. *Neth J Med*. 2007 Jun;65(6):215-7.

⁶ Kim DS et al. Pneumocystis carinii pneumonia associated with a rapid reduction of cortisol level in a patient with ectopic ACTH syndrome treated by octreotide and ketoconazole. *Exp Clin Endocrinol Diabetes*. 2001;108(2):146-50.

Immunosuppression – treatment with exogenous glucocorticoids

Dr. Zemskova described six adverse events related to exacerbation of an autoimmune disorder. This may be treatment-related in that mifepristone will block the immunosuppressive effects from exogenous steroid use. (b) (4)

during negotiations, the label was modified to contraindicate the use of Korlym in serious medical conditions in which steroids would be required (e.g., post-organ transplant). There may be certain medical conditions in which Korlym dose may be reduced or held for short courses of glucocorticoid therapy.

Other concerns of hypercortisolemia

The clinical and metabolic effects of Cushing's syndrome results for elevated cortisol levels which is not eliminated with Korlym. The effects of cortisol extend beyond that of glucose metabolism and include, but are not limited to, wound healing, bone differentiation and metabolism, lipid metabolism, and mineralocorticoid effects. These concerns could not be adequately assessed in this program given the trial design and size of the patient population but one effect of hypercortisolemia that was apparent in this program can be attributed to the binding of cortisol to the mineralocorticoid receptor. This effect was manifested as hypokalemia although the increased blood pressure might also be a consequence of hypercortisolemia although there was poor correlation of cortisol levels with HTN in this program. Another potential effect of cortisol on the mineralocorticoid receptor would relate to effects on myocardial tissues as the mineralocorticoid receptor is also expressed in cardiac myocytes and its activation has been associated with tissue damage in heart failure and post-MI patients.⁷ One patient in Study 400 developed worsening cardiomyopathy during treatment and had another episode after drug discontinuation. One other patient in Study 415 had developed mild heart failure responsive to diuretic therapy. Again, a causal association can not be established based on these two reports in this uncontrolled clinical trial. It should also be noted that improvement in heart failure was reported with mifepristone in the published literature and summarized in Dr. Zemskova's review.⁸ However, published literature also supports the potential role of glucocorticoid and RU486 on expansion of infarct area in rodent studies that is ameliorated by spironolactone.⁹ Although this clinical development can not provide any adequate CV risk assessment of Korlym or hypercortisolemia, it would be appropriate to include under the Warnings and Precautions section to use caution in patients with underlying heart disease including heart failure.

9. Advisory Committee Meeting

Korlym is not a new molecular entity requiring discussion before an advisory committee. However, it was acknowledged early in the review process that if approved, this would be a novel medical therapy for Cushing's syndrome and there may be concerns about expanded availability of mifepristone which is currently only available as Mifeprex under a restricted distribution program for medical termination of early term pregnancy.

⁷ Funder JW. Reconsidering the roles of the mineralocorticoid receptor. *Hypertension*. 2009; 53: 286-290.

⁸ Chu et al. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone. *J Clin Endocrinol Metab*. 2001; 86:3568-3573.

⁹ Mihailidou et al. Glucocorticoids activate cardiac mineralocorticoid receptors during experimental myocardial infarction. *Hypertension*. 2009; 54:1306-1312.

An advisory committee was not considered necessary to discuss the clinical development program as it was felt that the scope of the program for an orphan disease was not out of the ordinary. The selected efficacy endpoints were clinically relevant to the disease and scientifically sound based on the drug's mechanism of action. Similarly, the safety concerns predicted with the drug were also based on knowledge of the pharmacologic action. Review of the clinical studies did not yield any different conclusion.

The need for a restricted drug distribution plan is discussed under Section 13.

10. Pediatrics

Korlym was granted orphan drug status. Pediatric studies are therefore waived under PREA.

11. Other Relevant Regulatory Issues

(b) (4)

(b) (4)

(b) (4). FDA has already negotiated a more limited patient population with Korlym than was originally proposed by the applicant. The fact that cortisol levels cannot be relied on for the monitoring of clinical response and drug toxicity was known during the IND stage (b) (4). Given the limited availability of medical therapies, which themselves are used off-label with their own toxicities, I still conclude that with careful monitoring and cautious titration of Korlym by physicians experienced in the care of patients with Cushing's syndrome, a reasonable balance of benefit to risk can be achieved.

12. Labeling

One of the objectives of the prescriber and patient labeling is to convey that Korlym will cause pregnancy termination and that it is NOT to be used in a pregnant patient. To achieve this, multiple sections of labeling reiterate this as summarized below:

Prescriber labeling will include a BOXED WARNING

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.

Under CONTRAINDICATIONS Section 4.1 the label will state:

4.1 Pregnancy

Korlym is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with Korlym. Nonhormonal contraceptives should be used during and one month after stopping treatment in all women of childbearing potential. *[See Use in Specific Populations 8.8]*

Under USE IN SPECIFIC POPULATIONS 8.1 Pregnancy:

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)]*

Under PATIENT COUNSELING INFORMATION

17.1 Importance of Preventing Pregnancy

- Advise patients that Korlym will cause termination of pregnancy. Korlym is contraindicated in pregnant women.
- 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.

And the first item in the Medication Guide, What is the most important information I should know about Korlym is:

Korlym can cause serious side effects.

1. Loss of a pregnancy

For women who can become pregnant, you must:

- Have a negative pregnancy test:
 - before starting Korlym
 - before restarting Korlym if you stop taking it for more than 14 days
- Use a non-hormonal form of birth control during treatment with Korlym and for 1 month after stopping treatment. Talk to your doctor to find out how to prevent pregnancy. Tell your doctor right away if you think you may be pregnant.

FDA has also limited the indication to the smaller subset of patients with Cushing's syndrome as follows:

Korlym (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have diabetes mellitus type 2 or glucose intolerance and have failed surgery or are not candidates for surgery.

Please see the approved label accompanying the action letter as there are many other important risks and benefit information conveyed beyond pregnancy termination.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

When prescribed to the selected population of Cushing's syndrome who have diabetes or glucose intolerance AND have failed surgery or are not candidates for surgery, a benefit of Korlym therapy can be ascribed to the observed improvements in glucose control. In addition to a reduction in AUC_{glu} after an oral glucose challenge, a reduction in HbA_{1c} was also observed and several patients had reductions in anti-diabetic medication requirements. The long-term benefits of glucose control in this population are not known but expectation of such a demonstration for this indication is neither feasible nor reasonable given that the population indicated is circumscribed to those who have limited options. In most patients, the shortened life expectancy makes the concern of long-term benefits of glycemic control less paramount.

Korlym is not without risks, some being very serious due to the mechanism of action of the drug. Given that these risks are predictable, appropriate labeling and use of Korlym by specialists well-versed in the care of patients with Cushing's syndrome should allow safe and effective use for the indicated population.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The serious safety concerns associated with Korlym use for the treatment of adults with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance include adrenal insufficiency, hypokalemia, vaginal bleeding, potential for QT prolongation, and drug-drug interactions. These safety concerns and others identified in the product label can be managed effectively through prescriber labeling and a Medication Guide.

The safety concern in a pregnant woman is termination of her pregnancy. The likelihood that patients in the intended population will fall into this category is low. The hypercortisolemic state of these patients often results in amenorrhea and infertility through secondary hypogonadism. Chronic therapy of mifepristone at the doses necessary to control hypercortisolemia is also an effective contraceptive. For both these reasons, the probability that a Cushing's patient will become pregnant while on Korlym is very low. Regardless, the label will include a boxed warning and a contraindication for its use in pregnant women (Please see section 12 of memo). A contraindication is the most stringent safety warning in an FDA-approved labeling as under 21 CFR 201.57 it means that the risk from use of Korlym clearly outweighs any possible therapeutic benefit in the pregnant patient. The label will also recommend use of a nonhormonal contraceptive in women of childbearing potential during and for at least one month after stopping treatment with Korlym.

The concern that Korlym may be used intentionally by women seeking an abortion (off-label use) was also considered in the approval of this application and whether it would require a REMS with ETASU (restricted distribution) to prevent off-label use. Given that the safety concerns associated with Korlym in its intended population does not support a REMS with ETASU and that the patients are severely ill with limited options, it was determined that establishing a REMS with ETASU to prevent off-label use established an unnecessary hurdle for a patient population with a serious and life-threatening disease.

With the NDA submission, the applicant proposed to establish a distribution program through a central pharmacy under the Support Program for Access and Reimbursement for Korlym (SPARK). Physicians can submit their prescriptions through this central pharmacy to have Korlym delivered directly to the patient. Distribution through a central pharmacy not only ensures timely access to treatment because it is unlikely that many pharmacies will keep Korlym stocked for the few patients eligible for treatment (~5000) but it will also limit its availability for potential off-label use.

- Recommendation for other Postmarketing Requirements and Commitments

The applicant will have two PMRs:

1. conduct a DDI study between ketoconazole and mifepristone to characterize the effect of a potent CYP3A4 inhibitor on mifepristone exposures.
2. conduct a drug utilization study to better characterize reporting rates for adverse events of interest associated with chronic Korlym use.

The drug utilization study will provide a denominator for adverse events reported with the use of Korlym, thus allowing an estimate of reporting rates which can be assessed in the context of the known background incidence rates of these adverse events in the Cushing's population. The reports of these adverse events of interest (endometrial hyperplasia and/or vaginal bleeding, retinopathy, and major adverse cardiovascular events) will be gathered through enhanced pharmacovigilance (15-day expedited reporting). Additional information such as gender and age of patient, dose and duration of use, and prescriber specialty can also be obtained through the drug utilization study which will provide some insight on whether the population prescribed Korlym reflects the indicated use of the product. But in addition to the measures established to ensure access to Korlym to patients with Cushing's syndrome who have limited options, FDA will need to communicate to the public that this drug is contraindicated in pregnant patients. Those seeking to use the same active ingredient for pregnancy termination must obtain it through a different program designated by FDA to ensure the safe and effective use of Mifeprex for early medical termination of pregnancy.

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/s/

MARY H PARKS
02/17/2012