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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 # **Supplement #**	202107 (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-disclipine team leader (CDTL) memo has clearly outlined these discussions and the reader is also referred to memos written by DRISK reviewers, Drs. Robottom, 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:

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