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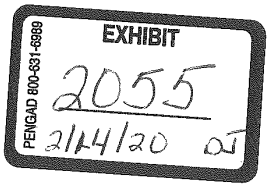
APPLICATION NUMBER:

202107Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW



Cross-Discipline Team Leader Review

Date	February 13, 2012
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA -202107
Applicant	Corcept Therapeutics Inc.
Date of Submission	April 15, 2011; received April 18, 2011.
PDUFA Goal Date	February 17, 2012
Proprietary Name / Established (USAN) names	Korlym /mifepristone
Dosage forms / Strength	Tablet/300 mg
Proposed Indication(s)	Treatment of hypercortisolism in patients with endogenous Cushing's syndrome
Recommended:	Approval

1. Introduction

On April 15, 2011 Corcept Therapeutics submitted a New Drug Application for Korlym (mifepristone) under Section 505(b)(2) of the Federal Food, Drug and Cosmetics Act in support of the following indications: treatment of clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome including, specifically, "patients with Cushing's disease who have not adequately responded to or relapsed after surgery", "patients with Cushing's disease who are not candidates for surgery". (b) (4) [redacted]. Mifepristone is a glucocorticoid receptor (GR-II) antagonist and the rationale for being used to treat hypercortisolism in Cushing's syndrome is based on its ability to compete with endogenous cortisol at the receptor level, and block the biological activity of cortisol. Korlym is manufactured as a 300 mg tablet and is intended for use once a day orally. Treatment with Korlym is initiated at 300 mg once a day and titrated up to 1200 mg daily based on clinical response and tolerability. Korlym is intended for chronic use. Currently there are no approved drug products for the treatment of Cushing's syndrome; several products are used off label alone or in combination with variable efficacy results.

The mifepristone clinical program for Cushing's syndrome was developed under IND 76,480, which was opened on August 2, 2007 in the Division of Metabolism and Endocrinology (DMEP). (b) (4) [redacted]. It should be noted that at the time of opening IND

76,480 for Cushing's syndrome, the Korlym pharmacology/toxicology and clinical pharmacology programs had been quite extensive, and human exposure across a variety of indications and doses exceeded 1100 subjects/patients. The IND was in fact opened with what was planned to be the registration clinical trial (Study C1073-400), the results of which are submitted in the current NDA. This study was planned as a 24-week, open-label, uncontrolled (single-arm), Phase 3 clinical trial to be conducted in 50 patients with Cushing's syndrome and glucose intolerance or diabetes (29 patients in the end) and hypertension (21 patients). Cushing's disease is a rare disease and Corcept has received orphan indication on July 5, 2007 for the "treatment of clinical manifestations of endogenous Cushing's syndrome". At the time when the IND was opened, DMEP provided answers to a series of questions submitted by the sponsor regarding the development program for the Cushing's syndrome indication. In summary:

- The Division agreed that the toxicology studies conducted up to that time, along with ongoing carcinogenicity studies, would be sufficient for a Cushing's syndrome indication.
- Given the rarity of the disease and the ethical issues raised by conducting a placebo controlled trial in a condition of such severity when there is preliminary evidence of efficacy from published reports, submission of a single Phase 3 clinical study using a single-arm, open-label design was found to be acceptable for an NDA submission.
- The Division provided advice regarding efficacy endpoints selected to be evaluated in the pivotal study, and specifically indicated that, due to the fact that cortisol levels cannot be used as a measure of efficacy in the case of mifepristone, the primary efficacy endpoints should be clinical, i.e. change in blood pressure and/or glycemic control. The Division also advised to use of area under the time vs. concentration curve for glucose during an oral glucose tolerance test as a study endpoint. In the end it was selected as one of the two primary endpoints.
- Following review of the dosing information accumulated in healthy volunteers and across various patient populations studied under mifepristone INDs, the Division recommended that Korlym doses should not exceed a maximum of 20 mg/kg/day.
- The Division also advised that every woman with an intact uterus undergo transvaginal ultrasound at baseline and completion of the study.

In subsequent correspondence (September, 2, 2009) the Division added a request to obtain baseline and end-of-trial endometrial biopsy in order to evaluate the proliferative effect of the drug on the endometrium. In doing so, the Division decided that, given the severity of the condition being studied and the lack of an approved therapy, the potential effects of mifepristone on reproduction should be studied in the registration clinical trial rather than in a dedicated reproductive study that will slow the Korlym clinical program.

In a communication dated March 3, 2010, DMEP asked the sponsor to add baseline and end-of-trial ophthalmological exams to the safety evaluations of the pivotal trial. This request was triggered by the observation of retinal atrophy in the preclinical program in a single animal species (Sprague Dawley rats) that was not confirmed in a second species (i.e. not observed in mouse or dog). As was the case with endometrial biopsies, this request and the subsequent implementation in the clinical trial were made while the trial was in progress.

It should be mentioned that after the initiation of the pivotal trial the sponsor noticed that the patients enrolled had baseline diastolic blood pressures lower than expected (b) (4) This issue and its implications will be discussed in detail in the efficacy section of this memorandum.

DMEP granted Corcept Therapeutics a pre-NDA meeting that took place on September 14, 2010. Issues discussed at the meeting included Corcept's program for the Cushing's syndrome indication in general, the sponsor's intention to follow a 505(b)(2) regulatory path, the format and content of the NDA, the proposed stability program, and a proposed REMS. With respect to the plan to submit an NDA under Section 505(b)(2) of the FD&C Act, the sponsor expressed their intension to cross reference the nonclinical data from another mifeprestone product (Mifeprex) as the listed drug. They were advised that the nonclinical toxicology studies conducted under IND 76,480 were sufficient to bridge to the nonclinical findings in the already-approved Mifeprex label. During the meeting, the Agency also provided advice to standard CMC, biopharmaceutics, and clinical pharmacology questions. There were no areas of disagreement and DMEP agreed with sponsor's overall plan.

2. Background

Important for establishing an accurate risk/benefit analysis for Korlym in Cushing's syndrome is a clear understanding of the patient population for which Korlym is intended for use, and the complex medical context in which the decision of adding Korlym to the management of patients with Cushing syndrome is made. Cushing's syndrome is a multisystem disorder of cortisol excess. Korlym aims at treating patients with endogenous hypercortisolism (exogenous hypercortisolism, the most frequent cause of Cushing's syndrome, is almost exclusively an iatrogenic condition and is treated by dose reduction or optimization). The hypercortisolism in endogenous Cushing's syndrome (further referred to in this memorandum simply as Cushing's syndrome), results from inappropriate activation of the hypothalamic-pituitary-adrenal (HPA) axis at either the hypothalamus or pituitary level, excess cortisol secretion originating from the adrenal gland (tumors, hyperplasia), or from ectopic sources of corticotropin releasing factor (CRF), adrenocorticotropic hormone (ACTH), or cortisol. By far the most common type of Cushing's syndrome is Cushing's disease, a condition which is due to excessive secretion of ACTH from a pituitary micro- or macroadenoma (it accounts for up to 80% of all cases of Cushion's syndrome).

(Endogenous) Cushing's syndrome is a rare disease. The incidence in the US ranges from 0.7 to 2.4 per 1 million persons per year[1]. With an estimated prevalence of approximately 20,000 patients, Cushing's syndrome meets the regulatory definition of a rare disorder, and, in fact,

[1] Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006 May 13;367 (9522):1605-17.

Korlym has received orphan designation. A disease of adult age mostly (peak incidence is between 25 and 40 years of age) that affects women more than men (8-fold higher rate of pituitary tumor and 5-fold higher rate of cortisol-secreting adrenal tumors in women with Cushing syndrome than in men), Cushing's syndrome, if left untreated, has an extremely poor prognosis: a mean duration from presentation to death of 4.7 years in Cushing's original series and a mortality rate that is 5-fold higher than that of age and gender-matched subjects[2]. Medical treatment of Cushing's syndrome is secondary to surgical management that can be curative. However, a significant proportion of patients is not cured by surgery. For instance, remission rates following initial surgery for Cushing's disease due to microadenomas of the pituitary are between 70-90% and smaller (50-65%) if due to macroadenomas[3]. Patients who fail surgery have several therapeutic options that include repeat surgery at the original site (pituitary or ectopic) or removal of the adrenals, radiotherapy, or medical therapy. Medical therapy may also be used rarely in some patients who are not candidates for surgery or radiotherapy (including patients with metastatic disease), or when immediate control of the hypercortisolemia is required prior to surgery due to the severity of the disease.

Currently there are no approved medical therapies for Cushing's syndrome. Several drugs that reduce cortisol secretion (adrenal-directed therapy) are used off label in clinical practice (metyrapone, etomidate, ketoconazole) with the goal of reduction or normalization of cortisol secretion. In many respects mifepristone stands alone in the context of the above-mentioned steroidogenesis inhibitors, because it does not reduce cortisol synthesis. Rather, mifepristone reduces the biological effects of the existing endogenous cortisol by competing effectively with it for binding to the type II nuclear glucocorticoid receptors for which mifepristone has an 18-fold higher affinity than cortisol.

The fact that the potential efficacy of mifepristone cannot be measured by quantifying endogenous cortisol secretion (e.g. measuring urinary free cortisol, an important efficacy measure in clinical practice and an equally relevant endpoint in clinical trials) has had direct consequences in the way clinical trials with Korlym have been planned and conducted. In absence of any other qualified biomarkers of disease improvement, the applicant had to select clinical endpoints. Of the many clinical manifestations of Cushing's disease (glucose intolerance and diabetes, hypertension, obesity, myopathy, bone loss, decreased quality of life, gonadal dysfunction, dermatological changes, compromised immune function, psychiatric symptoms, and fluid and electrolyte disturbances) glucose intolerance and diabetes, on one hand, and hypertension, on the other hand, were selected as primary measures of efficacy for the Korlym phase 3 clinical trial.

Thus, central to this application is whether the Korlym clinical program has provided substantial evidence of effectiveness in adults with Cushing syndrome who have not adequately responded to surgical treatment. This determination is a particularly challenging task for a variety of reasons. First and foremost, Korlym has been studied in a single-arm clinical trial with no comparator; since there are no approved medical therapies for this

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[2] Etxabe J, Vazquez JA 1994 Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf) 40:479–484

[3] Blevins LS et al. An approach to the management of patients with residual Cushing's disease. J Neurooncol (2009) 94; 313-319.

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