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APPLICATION NUMBER:

202107Orig1s000

PHARMACOLOGY REVIEW(S)

PHARM/TOX SUPERVISORY MEMO

Date:	7 Feb 2012
RE:	Korlym NDA 202107, 505(b)(2) application
Sponsor:	Corcept Therapeutics
Drug/Indication	Mifepristone / Hyperglyemia in Cushing's Syndrome

Corcept Therapeutics is seeking approval of Korlym for the treatment of hyperglycemia secondary to metabolic complications of endogenous Cushing's syndrome. Korlym is the proposed trade name for mifepristone which is a receptor antagonist for the glucocorticoid and progestin receptors. Anti-androgen activity is also a known effect of mifepristone. The intended therapeutic target for the proposed indication is the glucocorticoid receptor, though inhibition of the progestin receptor is certain to occur at therapeutic drug concentrations.

Corcept cites Mifeprex (NDA 20687) as the listed drug upon which to rely for part of the toxicological assessment of Korlym (i.e., 505b2), specifically the reproductive and developmental studies as described in the Pregnancy and related sections of the approved Mifeprex drug label. Reliance on Mifeprex for this information is scientifically valid based on studies conducted by Corcept that chemically identified Korlym as mifepristone, the same active ingredient in Mifeprex. Further, the toxicological profile of Korlym observed in two-year rodent bioassays and a twelve-month dog assay, along with associated dose-ranging studies, also conducted by Corcept, are consistent with the known pharmacology of mifepristone as a glucocorticoid and progestin receptor antagonist. Confirmation that the chemical identity and pharmacological/toxicological activity of Korylm is consistent with mifepristone provides sufficient information to bridge to Mifeprex as the listed drug.

As Mifeprex is approved for single-dose use, Corcept was obligated to characterize the chronic toxicology of Korlym in new studies to support the chronic clinical indication sought in Cushing's patients. Thus, the pivotal studies included a twelve-month dog study and two-year bioassays in rats and in mice. As described in Dr. Brundage's review, these animal species did not tolerate mifepristone at doses that were tolerated by human subjects in clinical trials. The absence of endocrine disruption at baseline in the test species likely explains the inability to test doses of mifepristone much above the intended clinical dose. At the doses tested, the observations made were consistent with the anticipated pharmacology and toxicology of an anti-glucocorticoid, anti-progestin, anti-androgen agent. The extensive and complex hepatic metabolism noted in animals likely underlies the treatment-related liver effects which ranged from hepatocellular enlargement and ALT elevation in rodents and dogs in shorter-term studies to liver adenomas and follicular cell thyroid adenoma and carcinoma in female rats exposed to mifepristone for two years. Complex hepatic metabolism is also seen in human subjects, and periodic transaminase monitoring may be a reasonable safety measure. Within the dosing

limitations discussed above, results of these studies adequately addressed the lack of chronic toxicology data with mifepristone and adequately support, in part, its proposed clinical use in Cushing's patients.

I concur with Dr. Brundage's recommendation of 'approval' for NDA 202107.

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

/s/

TODD M BOURCIER
02/07/2012
P/T recommends AP

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number:	202107
Supporting Document/s:	SDN 1
Applicant's Letter Date	15 April 2011
CDER Stamp Date:	18 April 2011
Product:	Korlym (Mifepristone Immediate-Release Tablet)
Indication:	Reduction of the effects of hypercortisolism in patients with endogenous Cushing's Syndrome
Applicant:	Corcept Therapeutics
Review Division:	Division of Metabolism and Endocrinology Products (HFD-510)
Reviewer:	Patricia Brundage, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
Division Director:	Mary Parks, M.D.
Project Manager:	Jena Weber

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