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APPLICATION NUMBER:

202107Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
MEMORANDUM
(Addendum to the original review dated to 1/13/2012)

NDA:202107	**Submission Date: April 18, 2011**
Brand Name	**Korlym™**
Generic Name	**Mifepristone**
Reviewer	**Jee Eun Lee, Ph.D.**
Team Leader (Acting)	**Jayabharathi Vaidyanathan, Ph.D.**
OCP Division	**Clinical Pharmacology II**
OND Division	**Metabolism and Endocrinology Products**
Sponsor	**Corcept Therapeutics**
Relevant IND, NDA	**NDA 20687 (Mifeprex); IND 76480 (Korlym)**
Submission Type	**Original NDA 505(b)(2)**
Formulation; Strength(s)	**Tablets for immediate release; 300 mg**
Route of Administration	**Oral**
Indication	**Cushing's syndrome for patients who have not adequately responded to surgery** (b) (4) [redacted]

This is an addendum to the Clinical Pharmacology Review for NDA 202107 dated 1/13/2012 and includes recommendations on the sponsor's proposed labeling.

Summary of Labeling Recommendations

'Strikethrough red' text is for statements recommended to be deleted and 'blue color' text is for statements recommended to be added.

(b) (4) [redacted]

9 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

JEE E LEE
01/23/2012

JAYABHARATHI VAIDYANATHAN
01/23/2012

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Division Director	**Chandrahas Sahajwalla, Ph.D.**
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Background:

Refer to Clinical Pharmacology review dated 1/13/12 in DARRTS for Clinical Pharmacology details of mifepristone. The purpose of this addendum is to summarize the Clinical Pharmacology related post marketing study requirement.

1. Phase IV Requirements

Mifepristone is a substrate of CYP 3A4 and its three major active metabolites are formed via CYP3A4-mediated metabolism. Sponsor conducted a drug-drug interaction study with cimetidine, a mild CYP3A inhibitor. There was no effect of cimetidine on mifepristone exposure. The effect of moderate or strong CYP3A inhibitors on the pharmacokinetics of mifepristone has not been evaluated. Sponsor has proposed to (b) (4) [redacted]. Since ketoconazole, [redacted]nical management of Cushing's disease, there is a high potential of its concomitant use with mifepristone. The degree of change in exposure of mifepristone when co-administered with strong CYP3A inhibitors is unknown and may present a safety risk or deprive the patients on strong inhibitors the use of Mifepristone due to lack of accurate knowledge of this potential drug

interaction. Thus, the quantitative data for effect of ketoconazole on the pharmacokinetics of mifepristone would be beneficial to the target populations. A drug-drug interaction study with ketoconazole is recommended as a Post Marketing Requirement (PMR). The goal of this study is to get a quantitative estimate of the change in exposure of mifepristone following co-administration with ketoconazole. Based on the results of this study, the effect of moderate CYP3A inhibitors on mifepristone pharmacokinetics may need to be addressed. This will help provide more therapeutic options available to Cushing's patients and appropriate labeling of mifepristone when co-administered with CYP3A inhibitors.

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