

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202107Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

RISK MANAGEMENT REVIEW

Date: January 27, 2012

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Drug Name: Korlym (mifepristone)

Dosage and Route: 300 mg tablets; by mouth

Application Type/Number: NDA 202-107

Applicant/sponsor: Corcept

OSE RCM #: 2011-2351

EXECUTIVE SUMMARY

The purpose of this review is to document DRISK's determination that a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is not necessary for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome.

Corcept submitted a 505(b)(2) application for approval of Korlym (mifepristone) for the treatment of the signs and symptoms of endogenous Cushing's syndrome. Mifepristone (Mifeprex) is currently approved for pregnancy termination with a REMS with ETASU. Based on FDA feedback provided at the September 14, 2010 pre-NDA meeting, Corcept proposed a REMS with ETASU with their NDA submission.

After extensive research and multiple discussions with the review team, DRISK and the Division of Metabolism and Endocrinology Products (DMEP) determined that:

- A REMS with ETASU is not necessary to ensure that the benefits outweigh the risks of Korlym *in the Cushing's population*.
- A REMS with ETASU for Korlym would not improve the benefit/risk balance for the intended use (Cushing's) population and would add burden.
- Use of Korlym outside of Cushing's syndrome cannot be prospectively quantified.

The REMS Oversight Committee and the Center Director provided additional guidance and affirmed that although a REMS is required for Mifeprex, a REMS for Korlym is not necessary to ensure that the benefits of the drug outweigh its risks at this time. Korlym's safety and drug utilization should use be monitored through post marketing requirements (PMR). If data indicate that the current approach compromises the integrity of the Mifeprex REMS and results in serious adverse events, or additional serious safety signals arise, further regulatory action must be considered.

1 INTRODUCTION

The purpose of this review is to document DRISK's determination that a REMS with ETASU is not necessary for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome.

1.1 BACKGROUND

Corcept submitted a 505(b)(2) application on April 15, 2011 for approval of Korlym (mifepristone) to treat the clinical and metabolic effects of hypercortisolism in adult patients (≥ 18 years of age) with endogenous Cushing's syndrome including:

- 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)

Korlym is manufactured as 300 mg tablets. The proposed dosing for the aforementioned indication is 300 to 1200 mg daily by mouth.

1.2 REGULATORY HISTORY

Mifepristone is currently marketed as Mifeprex and approved on September 28, 2000 under 21 CFR 314 Subpart H for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The approved dosing is 600¹ mg (three (3), 200 mg tablets) followed by misoprostol on Day 4. Since approval, mifepristone is available only through a restricted distribution program that requires prescribers to be enrolled to be able to order Mifeprex and should only be distributed to/through a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. Mifeprex is not distributed to or dispensed through retail pharmacies. The restricted distribution program was approved as a REMS on June 8, 2011.²

In 2007, Corcept initiated a clinical development program to evaluate the clinical benefit of mifepristone in patients with Cushing's syndrome and received orphan drug designation on July 5, 2007.

A pre-NDA meeting with Corcept was held on September 14, 2010. Corcept informed the FDA that they intended to submit a REMS and requested comments on the draft REMS. The FDA informed Corcept that for this NDA/indication, a REMS with restricted distribution would be necessary to address the risk of termination of pregnancy. The proposed REMS must be sufficient to maintain the integrity of the current Mifeprex restricted distribution program. The sponsor was instructed that a complete review of the proposed REMS, and REMS materials would be done in conjunction with the full clinical review after the NDA is submitted.

On April 15, 2011 Corcept submitted NDA 202107 for review with a proposed REMS.

2 MATERIALS REVIEWED

The following materials were reviewed:

- Weber J. Pre-NDA Meeting Preliminary Comments for September 14, 2010. Signed under IND 76480 on September 9, 2010 by Weber J.
- NDA 202107 submitted on April 15, 2011 and received on April 18, 2011 with a proposed REMS with ETASU.
- Bhatnagar U. Maternal Health Team review for Mifepristone. Signed September 15, 2011 by Bhatnagar U, Feibus K, and Mathis L.
- Greene P. Drug use review of Mifeprex. Signed September 19, 2011 by Greene P, Chai G, and Governale L.

¹ Standard practice is to dispense a single, 200 mg tablet of mifepristone, not 600 mg. In addition, the standard misoprostol dose is 800µg (4 tablets), not 400 µg.

² Mifepristone was included on the list of products deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

- November 3, 2011 Center Director Briefing on Mifepristone for Cushing’s syndrome. Signed into DAARTS for NDA 202107 on November 15, 2011 by Egan A.
- (b) (6) Division of Reproductive and Urology Products consult response. Signed November 18, 2011 by (b) (6).

3 RISK BENEFIT CHARACTERIZATION

3.1 CUSHING’S SYNDROME AND TREATMENT OPTIONS

Cushing’s syndrome is a serious, multisystem disorder that results from overproduction of cortisol by the adrenal glands. For those not cured by surgery, it is a chronic and debilitating condition.⁴ If left untreated, Cushing’s syndrome limits survival to 4 to 5 years following initial diagnosis.³

Surgical resection of the offending tumor remains first line treatment, and initial cure or remission is obtained in 65-85% of patients with Cushing’s disease.⁴ In cases that surgery only partially or temporarily controls glucocorticoid hypersecretion (or for patients who are not candidates for surgery),⁵ radiation and/or pharmacologic treatment is used for disease control. A two to three fold increase in mortality is observed in most studies and this excess mortality seems confined to patients in whom initial cure was *not* obtained (the indicated population for mifepristone).⁴

There is an unmet medical need for additional drug treatment options for Cushing’s syndrome. The following table lists the drug treatment options, none of which are approved for Cushing’s syndrome:^{2,6}

Steroidogenic inhibition	Adrenolytic	Neuromodulators of ACTH release	Glucocorticoid receptor antagonism
<ul style="list-style-type: none"> • Metyrapone (not available in US) • Aminogluthethimide (discontinued)[^] • Ketoconazole 	<ul style="list-style-type: none"> • Mitotane^{^^} • Etomidate 	<ul style="list-style-type: none"> • Cyproheptidine* • Bromocriptine* • Valproic acid* • Octreotide* 	<ul style="list-style-type: none"> • Mifepristone
<p>[^]Aminogluthethimide was approved in 1980 and indicated “for the the suppression of adrenal function in selected patients with Cushing’s syndrome.”</p> <p>^{^^}Mitotane was approved in 1970 and indicated for “the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types.”</p> <p>*Agent has <u>not</u> demonstrated consistent clinical efficacy.³</p>			

³ Gums JG, Smith JD. Adrenal Gland Disorders. Pharmacotherapy: A pathophysiologic approach. 4th ed. Ed Dipro JT. Stamford, Appleton & Lange, 1999. Print.

⁴ Steffensen C, Bak AM, Rubeck KZ, Jorgensen JO. Epidemiology of Cushing’s syndrome. Neuroendocrinology 2010;92(supp 1):1-5.

⁵ Johanssen S, Allolio B. Mifepristone (RU 486) in Cushing’s syndrome. Euro J Endocrin (2007)156; 561-569.

⁶ Heyn J, et al. Medical suppression of hypercortisolemia in Cushing’s syndrome with particular consideration for etomidate. Pituitary (online May 10, 2011).

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