CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

FDA 0292

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)

- 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]

Steriodogenic inhibition	Adrenolytic	Neuromodulators of ACTH release	Glucocorticoid receptor antagonism
• Metyrapone (not available in US) • Aminoglutethimide (discontinued)^ • Ketoconazole	• Mitotane^^ • Etomidate	• Cyproheptidine* • Bromocriptine* • Valproic acid* • Octreotide*	• Mifepristone
^Aminogluthethimide was approved in 1980 and indicated "for the the suppression of adrenal function in selected patients with Cushing's syndrome." ^^Mitotane was approved in 1970 and indicated for "the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types." *Agent has not demonstrated consistent clinical efficacy.[3]			

[3] Gums JG, Smith JD. Adrenal Gland Disorders. Pharmacotherapy: A pathophysiologic approach. 4th ed. Ed Dipiro 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).

3.1.1 Size of Population

Cushing's syndrome is a rare disorder with incidence ranging from 0.7 to 2.4 per 1 million persons per year.[7] Ninety percent of all cases of Cushing's syndrome occur during adulthood; the incidence of Cushing's syndrome in children is estimated at approximately 0.2 cases per 1 million persons per year.

It is estimated that at any given time there are approximately 20,000 patients with Cushing's syndrome in the U.S. The peak incidence of Cushing's syndrome due to an adrenal or pituitary tumor occurs in persons 25-40 years of age; females are 8 times more likely than males to develop hypercortisolemia from a pituitary tumor and 3 times more likely to develop a cortisol-secreting adrenal tumor.

In the US, it is estimated that approximately 5,000 patients would be considered candidates for treatment with Korlym.

3.2 EXPECTED DRUG BENEFIT

Mifepristone works by binding to glucocorticoid receptors, preventing cortisol from binding, and thereby blocking cortisol's activity and effects. It does not decrease the amount of circulating cortisol. It has a rapid onset of action (~90 minutes for peak plasma concentrations).

According to the sponsor in Study 400 (open label, 24 week prospective trial), 60% of the diabetes patients met the primary endpont of at least a 25% reduction in $AUC_{glucose}$, and antidiabetic medication use was reduced in half of the patients. The Data Review Board determined that 72% of patients met the secondary endpoint of a change in signs and symptoms at week 24.

Mifepristone may be used as an adjunct to radiation, palliative treatment, or when rapid onset of anti-glucocorticoid effect is required (e.g., psychosis).

3.3 DURATION OF TREATMENT

Cushing's syndrome that is not cured by surgery is a chronic condition. Patients may be treated indefinitely (weeks, months, years/decades) with mifepristone.

3.4 SEVERITY OF THE RISK

The observed risks (adverse events documented in the safety database; adrenal insufficiency, hyopkalemia, and endometrial hyperplasia) in patients with Cushing's syndrome were considered. After discussion with DMEP, we agree that these risks can be adequately addressed through labeling.

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

Two risks were identified that are anticipated to occur in the post-marketing setting. These risks were the focus of the risk management discussion.

3.4.1 Fetal Loss (unintended pregnancy termination)

3.4.1.1 Cushing's Syndrome Patients

Mifepristone blocks progesterone receptors at lower doses than necessary for glucocorticoid receptor inhibition. Therefore, the lowest treatment dose studied for the treatment of Cushing's syndrome is effective for terminating pregnancy. However, mifepristone alone is less effective for pregnancy termination when compared to the combined regimen mifepristone/prostaglandin.[8]

Women with Cushing's syndrome are not at substantial risk for fetal loss because they are unlikely to be pregnant. The review by the Maternal Health Team (MHT) states that amenorrhea and ovulatory disturbances are associated with untreated Cushing's syndrome and therefore pregnancy occurs "rarely" in this population. Pregnancy may occur in a small subset of patients with Cushing's syndrome who are of childbearing age. MHT recommends that this possibility be noted in labeling.[9]

At the time treatment is initated with mifepristone, a woman has a low likelihood of conception due to her underlying disease. During treatment, if she is not compliant with mifepristone treatment, she would be amenorrheic due to worsened disease condition. If she is compliant with medication, mifepristone would prevent a sustained pregnancy. Therefore, the risk of fetal loss before and during treatment in the intended patient population appears low.

Pregnancy tests were performed in Study 400 as part of enrollment and repeated after any significant interruption of treatment. No pregnancies were reported.

3.4.1.2 Non-Cushing's Syndrome Patients

There are a variety of uses for mifepristone (b) (4). It has been studied to treat the following:

(b) (4)

(b) (4).

[8] (b) (6) Division of Reproductive and Urology Products consult response. Signed November 18, 2011 by (b) (6).

[9] Bhatnagar U. Maternal Health Team review for Mifepristone. Signed September 15, 2011 by Bhatnagar U, Feibus K, and Mathis L.

At present, mifepristone is only commercially available in blister packages (3 pills per carton) that are sold through the Mifeprex REMS. If Korlym is approved without restrictions (e.g. REMS), mifepristone will be more readily available to treat females of child bearing potential with other chronic conditions. The extent of off-label use of mifepristone, for the above conditions, in the post-marketing setting is unknown.

3.4.2 Intended Termination of Pregnancy with Korlym

If Korlym is approved without a REMS with restricted distribution, there will be increased access to mifepristone. This could lead to 1) prescribers prescribing Korlym for the termination of pregnancy without following the safeguards that are in place for Mifeprex and/or 2) misuse, pilfering, and diversion of Korlym for the termination of pregnancy not under the supervision of a healthcare provider.

The risk mitigation tools for the Mifeprex REMS are physician certification and controlled access to assure safe use. A Mifeprex prescriber must agree that he/she meets the required qualifications to assure the drug is used safey and appropriately. Compliance with the REMS requirements is not enforced beyond a one-time completion of the enrollment form (e.g., signed Patient Agreements are not collected). The certification requirement is the tool that provides controlled access for Mifeprex. Without restricted distribution, a prescriber using Korlym for pregnancy termination would not have to attest to having certain skills, agree to document certain information/activities, or report adverse events. The patient would not receive a Patient Agreement or Mifeprex Medication Guide that would provide the most relevant and important information to her for pregnancy termination. The current REMS does not prevent use beyond 49 days gestation, termination of an ectopic pregnancy, bleeding, incomplete abortion, and infection.

In considering if there is increased potential for pilfering and misuse with Korlym, we note that Mifeprex is distributed only to medical facilities and dispensed to the patient in small quantities (a single tablet) by certified prescribers. Korlym will be distributed directly to patients, in larger quantities and each Korlym tablet is an effective dose for pregnancy termination. Moreover, Korlym is proposed to be packaged in bottles of 28 and 280, making diversion and pilfering presumably easier relative to the Mifeprex packaging. Similar to Korlym, there is potential for Mifeprex to be pilfered or diverted from a distribution facility, during shipping, or at the place of dispensing. Mifeprex has processes in place to prevent drug loss during distribution and shipping that can be done outside a REMS for Korlym. It is not known if clinics keep careful stock and dispensing records of Mifeprex.

3.5 Risk in Context of Drugs in Class and Among Other Drugs Used to Treat the Disease

There are no other glucocorticoid receptor antagonists approved in the U.S. for comparison.

Ketoconazole, metapyrone (not approved in U.S.), mitotane, etomidate are anti-corticolic drugs that are used for the treatment of Cushing's syndrome. Because these drugs have a

different mechanism of action, they are not associated with the same potential risks as mifepristone. These drugs are associated with serious risk(s) although none of these drugs have a REMS.

3.6 How the Risk(s) are Managed Across Other Products and/or Diseases

3.6.1 Fetal Loss

Other drug products are associated with fetal loss (e.g., methotrexate, misoprostol; see Attachment 1). At present, this risk is addressed through labeling for these drugs. There are no REMS approved that address only fetal loss without also the accompanying risk of birth defect.

3.6.2 Intended Termination of Pregnancy with Korlym

We identified two drugs, misoprostol and methotrexate, that are associated with a risk of pregnancy termination and are approved for other uses. See the table in Attachment 1. The extent to which misoprostol and methotrexate are used off-label to terminate pregnancy is unknown. With each drug, the risk of termination of pregnancy is managed through labeling (Contraindication, Boxed Warning) and neither product has a REMS.

3.6.3 Misuse

Misuse has been addressed in different ways as follows:

Voluntary Restricted Distribution:

- *Example: Egrifta/growth hormone*: Growth hormones are at risk for misuse and abuse. None of the growth hormone products have a REMS. However, the sponsor has voluntarily decided to distribute this product through a non-REMS restricted distribution system which allows tracking "of each box of Egrifta to determine the volume of product dispensed and evaluate if the projected number of boxes dispensed correlates with prescription use in the intended population."[10] Egrifta was approved in 2010 with no REMS and no PMR for monitoring drug use.

Required Restricted Distribution Program

- *Example: Xyrem*[11]
  - At the time Xyrem was initially approved in 2002, the Sponsor agreed as a condition of approval to distribute and dispense Xyrem through a primary and exclusive central pharmacy, implement a program to educate physicians and patients about the risks and benefits of Xyrem, fill the initial prescription only after the prescriber and patient received and read the educational materials, and maintain patient and prescribing physician registries.[12]

[10] LaCivita C. Review of REMS for Egrifta. Signed September 3, 2010.
[11] Xyrem 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.
[12] Choudhry Y. REMS Interim Comment Set #1. Signed August 1, 2011 by Choudhry Y and Worthy K.

3.6.4 Same Active Ingredient, Different Indication and Different Risk Management Approaches

The agency evaluates an active ingredient based on the risk benefit profile for the intended population. To date, the Agency has not required a REMS for a product based only on the fact that the active ingredient already has a REMS for one population. For example, denosumab was originally approved under two tradenames for different indications. Prolia was initially approved for the treatment for post-menopausal osteoporosis (PMO). At that time, a REMS for Prolia was required and approved consisting of a Medication Guide and communication plan to "inform healthcare providers about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw." Under the tradename Xgeva, denosumab was approved for prevention of skeletal-related events in patients with bone metastases from solid tumors. A REMS was not required given the resulting differences in the risk benefit profile when considering the patient populations (post-menopausal women vs cancer patients with bone metastases) and prescribing populations (internists vs oncologists).

3.7 PRODUCTS AFFECTED

Mifeprex (and pending generics) are potentially affected because they are or will only be available under a restrictive REMS.

4 RISK MANAGEMENT CONSIDERATIONS

The following factors are important to consider:

- Burden to the intended population

  It is important to ensure that the intended treatment population can receive Korlym in a timely, dependable manner in the least burdensome way. Any restrictions will impede access with little to no benefit to Cushing's syndrome population.

- Confidentiality/Privacy

  Confidentiality and patient privacy is a significant issue with Mifeprex. To what extent do stakeholders who make, distribute, dispense, prescribe, and use Korlym need protection from a confidentiality perspective?

  The purpose of a REMS is to ensure the benefits of the drug outweigh its risks. Confidentiality and concern regarding the safety of the prescribers, pharmacists, and patients does not meet criteria. Confidentiality can be maintained without a REMS. Privacy may be better maintained if there are no systems in place to track formally prescribers and patients. Risk to pharmacies that stock the drug should be considered but it is outside the purview of a REMS.

- Reproductive potential for various possible Korlym off-label use populations

As stated in section 3.4.1.2. above, there are a variety of uses for mifepristone (b) (4). The therapeutic areas included below are more likely to include females of reproductive potential than other uses (b) (4)). A formal epidemiologic review was not conducted to estimate of the proportion of females of reproductive potential for each use. However, the following observations and/or assumptions were made:

(b) (4)

The degree to which Korlym will be used off label for the above uses is unknown.

- Extent of current off-label use

  Current Mifeprex drug utilization information is not informative in predicting broader uses for Korlym. In the September 19, 2011 mifepristone drug use review using commercial databases was conducted, off-label use was described as "uncommon" based on information obtained through a *sample* of medical offices and outpatient clinics. Sales distribution data was not available. The lack of findings are not surprising given the design of the Mifeprex REMS.

5 RISK MANAGEMENT OPTIONS

DRISK analyzed more than six risk management options to address intended termination of pregnancy by:

- HCPs outside of Mifeprex REMS
- women who seek to terminate a pregnancy and are not under the care of an HCP

Ultimately, three options were considered.

1. No REMS and voluntary restricted distribution through specialty pharmacies/distributors

   This REMS option may minimize diversion and subsequent misuse by minimizing the number of pharmacies stocking and dispensing Korlym for outpatient use. This option is in alignment with DMEP and DRISK's assessment that a REMS is not necessary to assure the safe use of mifepristone for treating patients with Cushing's syndrome because we believe the likelihood that a Cushing's patient experiences "serious complications" relating to pregnancy termination are low.

This approach is also consistent with misoprostol and methotrexate, both of which are known abortifacents and do not have a REMS to address that risk. This approach is used to prevent misuse of the growth hormone products.

2. REMS with ETASU – dispensing through certified specialty pharmacies

   This REMS option may minimize diversion and subsequent misuse by minimizing the number of pharmacies stocking and dispensing Korlym for outpatient use. In addition, Corcept would be required to provide FDA an assessment of how the REMS is achieving its goals.

   This option does not address intended termination of pregnancy with Korlym.

3. REMS with ETASU – prescriber certification (agreement not to use for termination of pregnancy) and distribution through certified specialty pharmacies that are willing to track inventory

   This REMS option would minimize diversion and subsequent misuse as described above. In addition, certified pharmacies (for outpatient dispensing, not inpatient hospital pharmacies) would verify that prescribers were certified. Prescriber certification would consist of agreement not use Korlym for pregnancy termination. The addition of prescriber certification would address the risk of intended termination of pregnancy with Korlym.

These options assume that the safety labeling is maximized to address Korlym use in pregnancy.

6 DISCUSSION

The issue of how to address intended termination of pregnancy was discussed at the REMS Oversight Committee meeting on September 29, 2011 and at a Center Director Briefing on November 3, 2011.

DMEP and DRISK presented at both meetings that women with Cushing's syndrome are unlikely to be or become pregnant given the effects of their disease on the reproductive system and the effects of daily mifepristone treatment. Therefore, addressing the risk of fetal loss associated with Korlym was not discussed because 1) pregnancy is not a likely event in the intended population and; 2) the use of Korlym for "off-label" uses (in women more likely to be pregnant) is unknown and available data do not indicate that mifepristone would be first line treatment for any diseases or conditions at this time. For these reasons, there was general agreement that fetal loss can be adequately addressed through labeling and is not necessary to require additional safe use measures through a REMS at this time.

The team stated that for any risk management approach, it is important to ensure that the intended treatment population can receive Korlym in a timely, dependable manner in the least burdensome way. Any restrictions could impede access without benefit to the intended population.

The primary focus shifted to whether or not a REMS is necessary for Korlym to maintain the integrity of the Mifeprex REMS. While the absence of any restrictions on Korlym could undermine the safe use conditions required by the Mifeprex REMS, a number of other factors are important considerations including:

- The burden (reduced access, treatment delays) of a restrictive REMS to the Cushing's population without any benefit from the REMS for this population.
- Overall drug exposure and subsequent access is anticipated to be small given the small size of the intended use population and lack of a signal for substantially broader use.
- The sponsor's plan to distribute Korlym through a specialty pharmacy regardless of the REMS. If necessary, this provides the sponsor the ability to monitor use more closely.
- The cost - If the cost of this orphan product is substanial, it may be expensive to obtain and deter use for pregnancy termination as well as other off label uses. In addition, third party payors/reimbursement may play a substantial role in influencing prescribing behavior. It is unknown how much Korlym will cost and how cost will impact prescribing behavior.[13]

The need for some monitoring of use was discussed. Commercial drug use databases will not provide FDA with adequate estimates of Korlym use because Korlym will be dispensed through a specialty pharmacy. As noted above, using a single specialty pharmacy does allow the sponsor the ability to monitor use more closely through its business contract with the specialty pharmacy. Similarly, commercial drug use databases are not able to provide an accurate estimate of Mifeprex use due to how it is distributed and dispensed. The first REMS assessment for Mifeprex is due June 2012 which we anticipate will provide a baseline to quantify current Mifeprex use. Given these considerations and the discussion with the Center Director, we agree that a post-marketing requirement (PMR) study to obtain Korlym use data (age, gender, dose, duration of treatment) "to better characterize the incidence rates of adverse events with Korlym" is prudent. Monitoring drug use data for both Mifeprex and Korlym, in conjunction with reports of serious adverse events resulting from pregnancy terminations outside of the Mifeprex REMS, will be important factors in future regulatory action to address any compromise to the Mifeprex REMS.

7 CONCLUSION

A REMS for Korlym is not necessary to ensure that the benefits of the drug outweigh its risks at this time. We agree that it is prudent to monitor use through a PMR. If data indicate that this 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.

ATTACHMENTS

[13] Planned parenthood charges $300-800 for a medical abortion (includes diagnostic testing, mifepristone, and misoprostol).

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SUMMARY REVIEW

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.

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SUMMARY REVIEW

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

Postmarketing Requirements/Postmarketing Commitments: None.

Risk Evaluation and Mitigation Strategies (REMS): The Applicant proposed a REMS modification for the Mifeprex REMS program with the submission of this efficacy supplement. The review teams from the (b) (6) evaluated the current Mifeprex REMS program and the proposed REMS modifications to determine whether each Mifeprex REMS element remains necessary to ensure that the benefits of Mifeprex outweigh the risks. Factors that impacted the decision included findings from two REMS assessments (the more recent REMS assessment review was completed in October 2015), an unchanged safety profile, and published literature that documented adequate safeguards in clinical practice with the use of Mifeprex in a regimen with misoprostol.

The teams determined that the following REMS modifications were warranted:

1. Revisions to the Prescriber Agreement Form to reflect the new dosing regimen and to reflect current REMS formatting and language standards
2. Removal of the Medication Guide as a REMS element, as distribution of the Medication Guide is required under 21 CFR 208
3. Removal of the Patient Agreement as a Documentation of Safe Use Condition (ETASU D)
4. Updating of the REMS goals to reflect the above 3 changes.
5. Removal of the phrase "Under Federal law" from the Prescriber's Agreement
6. Replacing the term "licensed physician" with "healthcare provider who prescribes"

The above modifications to the Mifeprex REMS program were discussed with the (b) (6) (b) (6) on January 15, 2016, as per (b) (6) .

The (b) (6) concurred with conforming changes to the Prescriber's Agreement to reflect the new dosing regimen, and with removal of the Medication Guide from the REMS. The Medication Guide would remain a part of labeling to inform patients about the risks associated with Mifeprex use. The (b) (6) also concurred with revisions to the REMS goals to reflect these changes.

The (b) (6) concurred with the removal of the term "under Federal law". A rationale for the original inclusion of the phrase "Under Federal law" cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and it was decided that the phrase be removed from the Prescriber's Agreement.

The (b) (6) concurred with use of the term "healthcare providers who prescribe." To support a change in the REMS that would allow qualified healthcare providers other than physicians to prescribe Mifeprex through the Mifeprex REMS program, the Applicant provided information from over 3,200 women in randomized controlled trials and 596 women in prospective cohort studies comparing medical abortion care by physicians versus other providers (nurses or nurse midwives). These studies were conducted in a variety of settings (international, urban, rural, and low-resource). No differences in serious adverse events, ongoing pregnancy or incomplete abortion were identified between the groups. Given that providers other than physicians are providing family planning and abortion care under supervision and that the approved labeling and REMS program stipulate that prescribers must be able to refer patients for additional care, including surgical management, allowing these prescribers to participate in the Mifeprex REMS program is acceptable.

The (b) (6) also concurred with the teams' recommendation to remove the Patient Agreement (ETASU D) from the REMS although some (b) (6) members commented that additional support for the review team's rationale for this modification was needed. The review team's rationale for this change was:

APPEARS THIS WAY ON ORIGINAL

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and Informed Consent, and, more specifically with Mifeprex, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed.
- Medical abortion with Mifeprex is provided by a well-established group of organizations and their associated providers who are knowledgeable in this area of women's health. Their documents and guidelines cover all the safety information that also appears in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the direct supervision of a certified prescriber.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

The Mifeprex REMS program will have a modified ETASU REMS that will continue to ensure that Mifeprex can only be prescribed by certified prescribers and be dispensed to patients in certain healthcare settings, specifically, clinics, medical offices and hospitals. The Medication Guide will continue to be distributed to patients required under 21 CFR part 208. As required for all ETASU REMS, ongoing assessments of the Mifeprex REMS program will continue to ensure that the modified Mifeprex REMS program is meeting its goals.

13. Decision/Action/Risk Benefit Assessment

Decision:

All regulatory and scientific requirements have been adequately addressed in this efficacy supplement. Review teams involved in this supplement have recommended approval of the supplement from their disciplines' perspective. The submitted efficacy and safety information supported approval of the proposed dosing regimen through 70 days gestation, and other changes discussed in this summary memo. This supplement will receive an Approval action.

Benefit Risk Assessment:

This efficacy supplement provided substantial evidence of efficacy for the proposed dosing regimen through 70 days gestation. The efficacy findings were similar to those that led to the approval of the original dosing regimen in 2000. In addition, the submitted published literature supported other changes sought in this efficacy supplement that will

be reflected in labeling: 1) a more flexible time interval of 24 to 48 hours between Mifeprex and misoprostol administration, 2) the option of at home administration of misoprostol, 3) the option of repeat misoprostol dosing, if clinically indicated, 4) flexibility in the follow–up time frame of 7 to 14 days, and 5) permitting qualified healthcare providers other than physicians to prescribe Mifeprex.

The safety findings of the proposed dosing regimen were acceptable and were similar to those seen with the original dosing regimen approved in 2000.

After review of the REMS modifications proposed by the Sponsor, I concur with the clinical team and (b) (6) recommendations that:

1. The Medication Guide can be removed from the Mifeprex REMS program. The Medication Guide requirements under 21 CFR part 208 require the Medication Guide to be distributed to patients. Mifeprex will only be dispensed by a healthcare professional who will be knowledgeable and able to provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or follow-up that may be required as appropriate, and who will answer any questions the patient may have. In that setting, the Medication Guide will already be a required available tool for counseling. Therefore, given the existing requirements under 21 CFR part 208, I concur that there is no reason for the Medication Guide to specifically be a part of the REMS.

2. The Prescriber Agreement Form (ETASU A) as revised reflects current FDA format and content to conform to current REMS programs and reflect the labeling changes that will be approved in this supplement. I concur that the changes are acceptable.

3. Revision of the Mifeprex REMS goals (ETASU C) will adequately mitigate the risk of serious complications by requiring certification of healthcare providers who prescribe and ensuring the Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber.

4. Removal of the Patient Agreement Form (ETASU D): I concur with the clinical review team that the Patient Agreement Form, which requires a patient's signature, does not add to safe use conditions for the patient for this REMS and is a burden for patients. It is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent. The Patient Agreement Form contains duplicative information already provided by each healthcare provider or clinic. I believe that it is much more critical for the healthcare provider who orders or prescribes Mifeprex to provide and discuss informed consent derived from their own practice so that care can be individualized for the patient.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

MEDICAL REVIEW(S)

2.3 Availability of Proposed Active Ingredient in the United States

Mifepristone: The only other FDA approval for mifepristone is the product Korlym, approved under NDA 202107 on February 17, 2012 for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

2.4 Important Safety Issues with Consideration to Related Drugs

Korlym (mifepristone) is indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Korlym is taken in oral doses of 300 mg to 1200 mg daily. It is contraindicated in pregnancy, patients taking simvastatin, lovastatin and CYP3A substrates with narrow therapeutic ranges, patients on corticosteroids for lifesaving purposes, and women with unexplained vaginal bleeding or endometrial hyperplasia with atypia or endometrial carcinoma. The label[2] provides warnings and precautions regarding adrenal insufficiency, hypokalemia, vaginal bleeding and endometrial changes, QT prolongation, exacerbation or deterioration of conditions treated with corticosteroids, use of strong CYP3A inhibitors, and opportunistic infections with *Pneumocystis jiroveci* pneumonia in patients with Cushing's. Adverse reactions noted in ≥20% of patients in clinical trials with Korlym included nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite and endometrial hypertrophy.

Reviewer comment:

Some of the adverse events noted with Korlym are also seen with Mifeprex, such as nausea and vomiting. However, Korlym is taken in higher doses, in a chronic, daily fashion unlike the single 200 mg dose of Mifeprex that is the subject of this supplement; the rate of adverse events with Mifeprex is much lower.

Ella (ulipristal acetate) is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. The **ella** label[3] notes that in clinical trials, the most common adverse reactions (≥ 10%) in women receiving **ella** were headache (18% overall) and nausea (12% overall) and abdominal and upper abdominal pain (12% overall).

Due to **ella's** high affinity binding to the progesterone receptor, use of **ella** may reduce the contraceptive action of regular hormonal contraceptive methods. The label notes that after **ella** intake, menses sometimes occur earlier or later than expected by a few

[2] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202107s000lbl.pdf

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf

- For use with prostaglandin analogues for termination of pregnancy for medical reasons beyond the first trimester
- Labour induction in foetal death in utero[5]

The estimated cumulative use of Mifeprex in the US since the 2000 approval is 2.5 million uses. Estimated global occurence of MAB and SAB combined was 43.8 million abortionsin 2008 (Guttmacher Institute data)[6]. MAB has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare.[7] Medical abortion comprises 16.5% of all abortions in the US, 25.2% of all abortions at or before 9 weeks of gestation[1], and based on data from 40 reporting areas sending data to the CDC, 30.8% of all abortions at or before 8 weeks gestation (2012 data).[8] In 2011, approximately 239,400 medical abortions were performed, which was a 20% increase from 2008 data.[9] Data show that in the most recently reported 12 months (September 29, 2014-September 28, 2015), (b) (4) Mifeprex tablets were distributed in the US (NDA 20687 SD # 650, Annual Report-15, submitted October 09, 2015). Further, the vast majority of practitioners in the US who provide medical abortion services use a regimen other than the FDA-approved one. In 2008, Wiegerinck et al published a survey of members of the National Abortion Federation which showed that only 4% of facilities were using the current FDA-approved regimen.[10]

It is noteworthy that ten years ago, the combination of mifepristone and misoprostol for medical abortion was included on the World Health Organization (WHO) Model list of Essential Medicines for termination of pregnancy where legal and acceptable, up to 9 weeks of gestation.[11] Several other national and international organizations have also endorsed the safe use of medical abortion up to 9 and 10 weeks of gestation. This topic will be discussed thoroughly in the Efficacy and Safety Sections.

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[5] Mifegyne Summary of Product Characteristics. Exelgyn Laboratories- June 2013. *https://www.medicines.org.**uk**/emc/medicine/617*

[6] Sedgh G et al., Induced abortion: incidence and trends worldwide from 1995 to 2008. Lancet, 2012;379:625-32.

[7] Cleland K, Smith N. Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data. Contraception 2015;92:179-81.

[8] Pazol K, Creanga AA, Zane SB, Burley KD, Jamieson DJ. Abortion surveillance--United States, Centers for Disease Control and Prevention (CDC). MMWR Surveill Summ 2012;61(SS-8):1–44 and Surveillance Summaries Nov 27, 2015; 64(SS10);1-40.

[9] Jones RK, Jerman J. Abortion incidence and service availability in the United States, 2011. Perspectives on Sexual and Reproductive Health 2014;46(1):3-14.doi10.1363/46e0414.

[10] Wiegerinck MMJ, Jones HE, O'Connell, K, Lichtenberg ES, Paul M, Westhoff CL. Medical abortion practices: a survey of National Abortion Federation members in the United States. Contraception 2008;78:486-491.

[11] World Health Organization April 2015 Model Lists of Essential Medicines Available online at http://www.who.int/medicines/publications/essentialmedicines/en/.

6.1.14 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. Return to fertility is well-documented: in the Patient Counseling Information section, the labeling states "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses" and "inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before she resumes sexual intercourse."

6.1.15 Additional Efficacy Issues/Analyses

The Applicant has requested that revised labeling provide only for the new proposed regimen and that the original approved regimen be deleted.

Reviewer Final Recommendation:

While there are no safety or efficacy reasons that would lead us to withdraw approval of the currently labeled dosing regimen, we concur that it may be deleted from labeling because very few providers currently use it, and inclusion of two options for dosing could be confusing. Of note, PPFA and NAF guidelines have used mifepristone 200 mg oral and misoprostol 800 mcg (initially given vaginally and now buccally) since 2001.

7 Review of Safety

Safety Summary

- Medical abortion with the new proposed regimen of Mifeprex 200 mg followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation is safe. Major adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are reported rarely in the literature on over 30,000 patients. The rates, when noted, are exceedingly rare, generally far below 0.1% for any individual adverse event. The number of postmarketing deaths associated with Mifeprex pharmacovigilance is very low. Non-vaginal routes of administration of misoprostol have increased and since the *C. sordellii* deaths associated with vaginal misoprostol, there have been no *C. sordellii* deaths. Given that the numbers of these adverse events appear to be stable or decreased over time, it is likely that these serious adverse events will remain acceptably low.

- Common adverse events associated with medical abortion occur at varying but acceptable rates.

- There are scarce cases of uterine rupture associated with early medical abortion. Medical abortion using mifepristone with or without misoprostol in the first trimester is safe from this perspective.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

FDA 0673

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

DATE: March 28, 2016

FROM: Janet Woodcock, MD
Director, Center for Drug Evaluation and Research

THRU: (b) (6)

TO: (b) (6)

RE: NDA 020687, Supp 20

The currently approved REMS for Mifeprex contains a Patient Agreement Form required to be signed by both the patient and the prescriber. During the review of the REMS in connection with supplement 20 to NDA 020687 submitted by the sponsor, (b) (6) found that the information contained in the Patient Agreement Form is generally duplicative of information in the Medication Guide and of information and counseling provided to patients under standard informed consent practices for medical care and under professional practice guidelines. For the reasons further described in their reviews, the reviewers recommended that the Patient Agreement Form be removed from the REMS.

After being briefed on the planned changes to the NDA that the Center was considering, the Commissioner concluded that continuing the REMS requirement for a signed Patient Agreement Form would not interfere with access and would provide additional assurance that the patient is aware of the nature of the procedure, its risks, and the need for appropriate follow-up care. He requested that the Patient Agreement Form be retained as an element of the REMS.

Therefore, I have asked (b) (6) and (b) (6) to continue to include a Patient Agreement Form in the REMS for Mifeprex.

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Modification

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

(b) (6)

(b) (6)

NDA: 020687
PRODUCT: Mifeprex (mifepristone) oral tablets
APPLICANT: Danco Laboratories (Danco)
FROM: (b) (6)
DATE: March 29, 2016

This memorandum provides the (b) (6) ((b) (6) review of the proposed modifications to the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) addressed in the (b) (6) ((b) (6) REMS Modification Review and Addendum to REMS Modification Review. A REMS for Mifeprex was approved on June 8, 2011, to ensure the benefits of the drug outweighed the risks of serious complications. The Mifeprex REMS consists of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Mifeprex was approved for the medical termination of an intrauterine pregnancy through 49 days of gestation on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (Subpart H). It was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the 2007 Food and Drug Administration Amendments Act. A formal REMS proposal was submitted by Danco and approved on June 8, 2011. The goals and elements of the approved Mifeprex REMS are briefly summarized in Table 1 below.

Table 1. Summary of Mifeprex REMS[1]

REMS Goals	To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
	To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.
REMS Elements	Medication Guide
	ETASU A – Special certification of healthcare providers (HCPs) who prescribe Mifeprex: Completion of Prescriber's Agreement form and enrollment in the REMS program.
	ETASU C – Mifeprex is dispensed only in certain healthcare settings: It is only available to be dispensed in clinics, medical offices or hospitals, under the supervision of a specially certified prescriber. Mifeprex will not be distributed to or dispensed through retail pharmacies.
	ETASU D – Safe-use conditions: Patients must complete and sign the Patient Agreement form that is to be placed in the patient's medical record. A copy of the Patient Agreement form and Medication Guide must be provided to the patient.
Implementation System	Distributors of Mifeprex must be certified and agree to ship Mifeprex only to locations identified by certified prescribers. Distributors must agree to maintain secure and confidential records, as well as, follow all distribution guidelines concerning storage, shipments and controlled returns.

[1] Source: The (b) (6) REMS Modification Review (NDA 20867/S-020, dated March 29, 2016), Table 1.

On May 29, 2015, Danco submitted an efficacy supplement (S-020) that proposed modifications to the Mifeprex Prescribing Information and REMS. In the S-020 submission, Danco seeks the following major changes (among others):

- (b) (4) dosing regimen of Mifeprex and misoprostol
- Extension of maximum gestational age from 49 days to 70 days
- Replacement of the term "licensed physician" with "(b) (4) in the REMS Prescriber's Agreement form
- Removal of the phrase "Under Federal Law" from the REMS Prescriber's Agreement form
- Revisions to the Patient Agreement form reflecting changes to the Prescribing Information

The proposed changes in the efficacy supplement prompted revisions to the Mifeprex REMS materials and also updating of the REMS materials to current format. During review of this efficacy supplement, we also evaluated the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure the drug benefits outweigh the risks. The Agency considered the recent (b) (6) REMS Assessment review completed October 13, 2015, safety data gathered since drug approval in 2000, and experience from current clinical practice to support additional modifications to the Mifeprex REMS.

After consultations between the (b) (6) and (b) (6) and considering the (b) (6) REMS Modification Review and Addendum to the REMS Modification Review, (b) (6) has determined that the approved REMS for Mifeprex should be modified as follows:

1. Revisions to the Prescriber's Agreement form in addition to those proposed by the Applicant
2. Removal of the Medication Guide as a REMS element
3. Removal of the Patient Agreement form as a Documentation of Safe Use Condition (ETASU D)
4. Updating of REMS goals to reflect the above changes

We concur with (b) (6) recommendation that the Prescriber's Agreement form should include other modifications to reflect current REMS standards and materials and also to reflect changes to align with approval of the efficacy supplement S-020, such as the dose and dose regimen and upper limit of gestational age.

In addition, we agree with Danco's proposed removal of the phrase "Under Federal Law," because of the lack of precedent for requiring such text and clinical rationale for its inclusion. As approvals and REMS are governed by Federal law, the phrase "Under Federal law" is unnecessary. Regarding Danco's proposal to replace "licensed physician," we have determined that the replacement term should be "licensed healthcare providers who prescribe," to include other practitioners who prescribe; in addition, this phrase is consistent with language in the statute.

We concur with (b) (6) recommendation that the Medication Guide is no longer necessary as an element of the REMS to ensure the benefits of Mifeprex outweigh its risks. The Medication Guide will continue to be part of the approved labeling that must be provided to a patient in accordance with 21 CFR part 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

In addition, we concur with (b) (6) recommendation that the signed Patient Agreement form is no longer necessary and should be removed as a condition of safe use (ETASU D). Recent professional guidelines for women seeking surgical and medical abortion services emphasize comprehensive counseling, education about the risks of different treatments, and obtaining and documenting informed consent.[2,3] The National Abortion

[2] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

Federation (NAF) clinical practice guidelines include a standard stating that documentation must show that the patient affirms that she understands the procedure and its alternatives, the potential risks and benefits, and that her decision is voluntary.[4] Approximately (b)(4)% of the use of Mifeprex in the U.S. is through Planned Parenthood Federation of America (PPFA)- and NAF-affiliated members, where patient counseling and informed consent is standard of care. The practice of treating women with Mifeprex is well-established by these organizations and their associated providers who choose to provide this care to women. In addition, the Medication Guide, which must be provided to the patient under 21 CFR part 208, contains the same risk information contained in the Patient Agreement form.

The safety profile of Mifeprex is well-characterized and its risks well-understood after more than 15 years of marketing. Serious adverse events are rare and the safety profile of Mifeprex has not substantially changed.[5] The removal of the Medication Guide as a REMS element and of the Patient Agreement form is not expected to adversely impact the ability of the REMS to ensure that the drug benefits outweigh its risks. The benefit-risk balance of Mifeprex remains favorable in the presence of the following:

- Retention of ETASUs A and C in the Mifeprex REMS: The Prescriber's Agreement form required for prescriber certification under ETASU A will continue to require that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This ensures that Mifeprex can only be dispensed by or under the direct supervision of a certified prescriber.

- Communication of risks through patient labeling: The Medication Guide, which will be retained as part of labeling, contains the same risk information covered under the Patient Agreement form. Under 21CFR 208.24, prescribers who dispense Mifeprex are required to provide the Medication Guide to patients. The Prescriber's Agreement form also reminds the prescriber to provide the Medication Guide to the patient.

- Information from published articles on established clinical practices: This information, including clinical guidelines and publications, indicates that comprehensive patient counseling and informed consent prior to medical or surgical abortion treatment is standard of care when using Mifeprex.

We have also determined that the information in the efficacy supplement supports changes to the goals of the Mifeprex REMS. We concur with (b)(6) recommendation that the REMS goals should be modified from:

A. To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
B. To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.

to:

The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:

a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.

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[3] National Abortion Federation Membership information accessed on the internet at http://prochoice.org/health-care-professionals/naf-membership/ on March 11, 2016
[4] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf on March 11, 2016.
[5] (b)(6) Mifeprex Post-marketing Safety Review, dated August 20, 2015.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

(b) (6)

(b) (6)

REMS MODIFICATION REVIEW

Date:	March 29, 2016
Reviewer:	(b) (4) (b) (6)
(b) (6)	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
Subject:	Proposed REMS Modifications
Drug Name(s):	Mifeprex® (mifepristone)
Therapeutic class:	Progesterone-receptor modulator
Dosage forms:	200 mg tablets
(b) (6) Review Division:	(b) (6)
Application Type/Number:	NDA 020687, Supp 20
Applicant/sponsor:	Danco Laboratories
(b) (6) (b) (6) #:	2015-1719

changing the name of the form from "Prescriber's Agreement" to "Prescriber Agreement Form" to be consistent with the terminology used in other similar REMS Programs. The term *"physician"* should be replaced, as proposed by the Sponsor. However the review team recommends the phrase "*healthcare provider who prescribes*" in lieu of the Sponsor proposed "(b) (4) to more closely reflect the statutory provision, and to align with this revision in the Mifeprex Prescribing Information (PI), which was based on information in the supplement.[4] Additional changes are intended to improve the flow of the document. See the appended, redlined document for further details.

Consistent with the labeling revisions in the efficacy supplement, the language in the Prescriber Enrollment Form about the gestational age should be changed to match the labeling being approved.

5.1.3. DRUG DISPENSED ONLY IN CERTAIN HEALTH CARE SETTINGS - ETASU C

No changes to ETASU C are proposed.

5.1.4. DOCUMENTATION OF SAFE USE CONDITIONS - ETASU D

5.1.4.1. PATIENT AGREEMENT

Per the Mifeprex REMS, a Patient Agreement form is required to be signed and placed in the patient's medical record as documentation of safe use conditions for Mifeprex. The review team recommends removal of the Patient Agreement form from the Mifeprex REMS. This recommendation is based in part on the fact that the current Patient Agreement is duplicative of the informed consent and counseling processes that take place in the US, consistent with medical standard of care and current clinical practice guidelines for abortion providers.[5,6,7] For example, the National Abortion Federation (NAF) clinical practice guidelines state that "obtaining informed consent and assessing that the decision to have an abortion is made freely by the patient are essential parts of the abortion process." The NAF guidelines also include a standard stating that documentation must show that the patient affirms that she understands the procedure and its alternatives, the potential risks and benefits, and that her decision is voluntary.[6] The NAF is a professional association; a condition of membership requires periodic quality assurance site visits, and members must agree to adhere to the Clinical Policy Guidelines published by the NAF.[7] When healthcare providers at NAF affiliated facilities were surveyed, between 96 and 99% of healthcare providers indicated they provided patient counseling and obtained and documented informed consent.[8,9] The review team is aware that

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[4] (b) (6) draft Clinical Review for Mifeprex (NDA 020687) PAS 20. Dated: March 29, 2016

[5] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

[6] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf on March 9, 2016.

[7] National Abortion Federation Membership information accessed on the internet at http://prochoice.org/health-care-professionals/naf-membership/ on March 9, 2016

[8] Gould H, Perrucci A, Barar R, Sinkford D, Foster D. Patient Education and Emotional Support Practices in Abortion Care Facilities in the United States. Women's Health Issues 2012; 22-4; 359-364

Planned Parenthood of America has informed consent forms describing the risks associated with medical abortions. The NAF affiliated members and Planned Parenthood of America facilities account for (b)(4)% of Mifeprex use.

The information in the Mifeprex REMS Patient Agreement form is duplicative of the informed consent process that is followed and documented by these providers, who also provide abortion counseling and education about adverse events. Additionally, the MG, which is required to be provided under 21 CFR 208, contains the same risk information addressed in the Patient Agreement form and will be provided at the time the medication is dispensed to the patient. Based on this information, the Patient Agreement form is not necessary to ensure the benefits outweigh the risks of Mifeprex.

Finally, the U.S. marketing history of Mifeprex spans over fifteen years. During this period of surveillance, the safety profile of Mifeprex has been well-characterized, and serious adverse events have rarely occurred. [10,11,12]

5.2. REMS DOCUMENT

The REMS document is being revised to reflect the changes described above as well as to reflect the Agency's current thinking on the language and flow in REMS documents. The changes to the different sections of the REMS document are described further below. For additional details, see the redlined and clean REMS document appended to this review.

5.2.1. GOALS

The review team is recommending modification of the Mifeprex REMS goals. Currently the goals are (A) to provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and (B) to minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. Since (b) (6) is recommending removal of the Patient Agreement from the REMS, (b) (6) recommends revising the REMS goals to reflect this change. The revised goal is to ensure that prescribers are aware of the risks of serious complications associated with the use of Mifeprex and that it can only be dispensed in certain health care settings. The goal would be modified to read:

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[9] O'Connell K, Jones HE, Simon M, Saporta V, Paul M, Lichtenberg ES. First trimester surgical abortion practices: a survey of National Abortion Federation members. Contraception 2009; 79:385-392

[10] (b) (6) ((b) (6) Mifeprex Post-marketing Safety Review: (b) (6), dated August 20, 2015

[11] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

[12] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

MAR 29 2016

Donna Harrison, M.D.
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1015 Fifteenth St., NW
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Washington, DC 20005

Re: Docket No. FDA-2002-P-0364

Dear Drs. Harrison and Rudd and Ms. Nance:

This letter responds to your citizen petition submitted on August 20, 2002, to the Food and Drug Administration (FDA or Agency) on behalf of the American Association of Pro Life Obstetricians and Gynecologists (AAPLOG), the Christian Medical Association (CMA) (n/k/a the Christian Medical and Dental Associations), and Concerned Women for America (CWA) (Petition).[1] Your Petition requests that the Agency stay FDA's approval of Mifeprex (mifepristone, also known as RU-486), thereby halting the distribution and marketing of the drug pending final action on the Petition. The Petition also requests that the Agency revoke FDA's approval of Mifeprex and requests a full audit of the French and U.S. clinical trials submitted in support of the new drug application (NDA) for Mifeprex.

We have carefully considered the information submitted in your Petition, comments on your Petition submitted to the docket, other submissions to the docket, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your Petition is denied.

[1] The citizen petition was originally assigned docket number 2002P-0377/CP1. The number was changed to FDA-2002-P-0364 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This citizen petition was submitted by AAPLOG, CMA, and Sandy Rios, the then-President of CWA. We have addressed this response to CWA's current CEO and President, Penny Young Nance.

[With respect to ectopic pregnancy:]

> MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.
>
> Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

The Agency has regularly completed a cumulative summary of U.S. postmarketing adverse events reported for the use of mifepristone for medical termination of pregnancy. From the approval date of Mifeprex (September 28, 2000) through October 31, 2012, we received 2,740 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy,[66] including 57 reports of severe infections[67] and 416 incidences of blood loss requiring transfusion. From November 1, 2012, through April 30, 2015, we received 984 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy, including 9 reports of severe bacterial infections and 134 incidences of blood loss requiring transfusion.[68] As of April 30, 2015, 89 ectopic pregnancies associated with the use of mifepristone in the United States had been reported since the approval of Mifeprex. As of July 24, 2015, 17 U.S. deaths had been reported since the approval of Mifeprex. Deaths were associated with sepsis in 8 of the 17 reported fatalities (7 cases tested positive for *Clostridium sordellii*, and 1 case tested positive for *Clostridium perfringens*).[69] Seven of the eight fatal sepsis case reported vaginal misoprostol use;

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[66] This represents data from the FDA's previous adverse event reporting system, which was known as AERS.

[67] Severe infections generally involve death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

[68] This represents data from the current FDA Adverse Event Reporting System (FAERS), which was implemented in September 2012 and replaced AERS. FDA migrated all of the data from the previous reporting system (AERS) to FAERS. FDA validated and recoded product information as the reports from the AERS database were migrated to the FAERS database. In addition, the FAERS database features a new search functionality that is based on the date FDA initially received for the case; this facilitates more accurate follow-up for cases that have multiple reports and multiple receipt dates. For these reasons, there may be differences in the case counts between AERS and FAERS.

[69] We note your statements in your October 10, 2003, Response to Opposition Comments that the presence of retained products of conception can lead to the development of intrauterine or systemic infection and that Mifeprex might potentiate this possibility through negative effects on immune system function or normal protective mechanisms (Response to Opposition at 17). Regarding retained products of conception and the emergence of infections, based on autopsy and/or ultrasound reports, there were no retained products of conception in any of the eight deaths associated with infections (sepsis). With respect to your claim that Mifeprex might increase the likelihood of infection by adversely affecting immune system function, although

one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a delayed onset of toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. In the ninth case, infection was ruled out and the final autopsy report listed pulmonary emphysema as the cause of death. [70]

We disagree with your assertion that adverse event reporting for Mifeprex is "spotty" and that, as a result, the database for post-approval adverse events for Mifeprex is incomplete (Response to Opposition at 18). You are correct that reporting to the Agency's MedWatch program is voluntary, and we acknowledge that there is always a possibility with any drug that some adverse events are not being reported. We believe, however, that the potential for underreporting of serious adverse events associated with the use of Mifeprex for medical abortion has been very low because of the restricted distribution of the product and because healthcare providers have agreed in writing to report any hospitalizations, transfusions, or other serious adverse events associated with the drug to the sponsor, which is required under FDA's regulations to report all adverse events, including serious adverse events, to the Agency (see 21 CFR 314.80, 314.81). As with all drugs, we will continue to closely monitor the postmarketing safety data on Mifeprex.

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published experimental data from animal models suggest that this is a theoretical possibility, the overall event rate of serious infections does not support this. If Mifeprex were adversely affecting immune system function, we would expect to see a much higher rate of serious infections from more common organisms, as well as a higher number of deaths in Europe (where mifepristone has been approved for over 24 years) and in the United States. Contrary to your statements, data from the medical literature and findings by the CDC suggest that the critical risk factor in the reported cases of sepsis is pregnancy itself (see Miech, RP, 2005, Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*, Ann Pharmacother, 39:1483-1488). In May 2006, FDA, along with the CDC and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health held a workshop on emerging clostridial disease. The issue of immunosuppression also was discussed at length during this public workshop. It was clear from the presentations at the workshop that *C. sordellii* causes rapid and serious clinical illness in settings other than medical abortion, including among pregnant women who have recently undergone spontaneous abortion or term delivery. The fact that cases of *C. sordellii* have been identified both in pregnant women who have undergone medical abortion and those who have not supports the idea that the physiology of pregnancy may be a more plausible risk factor for *C. sordellii* illness than having undergone a medical abortion with Mifeprex.

[70] FDA is aware of 11 additional deaths of women in foreign countries who used mifepristone for the termination of pregnancy. This included one death associated with sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial, and 10 deaths identified from post-marketing data. These 10 fatal cases were associated with the following: sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure"; thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes a jejunostomy feeding tube, and severe cystic fibrosis; *Clostridium septicum* sepsis (from a published literature report).

1 of 2 DOCUMENTS

The Pink Sheet

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June 12, 2000

SECTION: THE NEWS THIS WEEK

LENGTH: 631 words

TITLE: RU-486 ACTION DATE IS SEPT. 30; ALLEN NAMED REPRODUCTIVE DIVISION DIRECTOR

TEXT:

The Population Council anticipates FDA action on its pending mifepristone NDA by Sept. 30.

Following receipt of a second "approvable" letter in February from FDA for the oral abortifacient known as RU-486, the Population Council and its distribution/marketing partner Danco submitted a response to the agency at the end of March.

FDA issued the first "approvable" letter for mifepristone in September 1996.

The Sept. 30 action date for RU-486 indicates that the response being considered by FDA is a "Class 2" submission requiring substantial review work, which according to Prescription Drug User Fee Act guidelines is given a six-month review time.

The Population Council has not disclosed specifics regarding what additional information the agency requested in its February approvable letter, but stated that "some of the FDA's recent proposals are more restrictive than we had expected."

The organization said that the letter addressed labeling, manufacturing and distribution issues related to mifepristone. The Population Council noted that there will likely be Phase IV commitments with approval.

The agency's RU-486 distribution demands reflect FDA's recent emphasis on risk management (see related story, p. 12).

The politically charged nature of the product makes it an obvious candidate for a careful roll-out because of the potentially far-reaching consequences if safety concerns emerged.

Additional clinical trial data does not appear to be an issue holding up the review. The Population Council has no ongoing trials, although Abortion Rights Mobilization is conducting a treatment IND for the drug.

Danco and The Population Council submitted an updated proposed distribution plan to FDA prior to receipt of the approvable letter, and included the plan

2000 F-D-C Reports, Inc., The Pink Sheet, June 12, 2000

again in its March response to the agency, the organizations said.

Danco reported that distribution discussions with FDA are at a very early stage, and communication with the agency is frequent and ongoing.

At the time of the 1996 advisory committee review of mifepristone, The Population Council said it planned to distribute the pregnancy termination pill only to physicians trained in surgical abortion.

During the advisory committee meeting, Advanced Health Technology, a not-for-profit company licensed to distribute, manufacture and market the product, said it would offer training in surgical abortion to facilitate availability of the product.

Advanced Health Technologies has since transitioned into Neogen and now Danco. The group is essentially the same, Danco and the Population Council said, with some management and investor changes.

At the committee meeting, then-CEO of Advanced Health Technologies Susan Allen, MD, emphasized the practicality of training physicians to conduct surgical abortion, citing her own experience.

Allen is now at FDA, and will become permanent director of FDA's Reproductive & Urologic Drug Products Division effective June 18.

Allen has been acting division director since January, following the appointment of Lisa Rarick, MD, as deputy director of the Office of Drug Evaluation II ("The Pink Sheet" Dec. 20, 1999, p. 25). Allen joined the division as a medical officer in 1998, and became medical team leader for reproductive drugs in January 1999.

Allen is presumably recused from the mifepristone review as a result of her prior experience with the product.

Mifepristone first became available in France in 1989, where it is manufactured by a division of Hoechst Marion Roussel, now Aventis.

The Population Council was given U.S. rights to the drug in 1994 under an agreement brokered by the Clinton Administration. Though the application has been "approvable" since 1996, difficulties retaining a manufacturer have held up approval of the product.

LOAD-DATE: June 19, 2000

June 8, 2000, Thursday

F.D.A. Adds Hurdles in Approval of Abortion Pill

By SHERYL GAY STOLBERG

The long-running effort to bring the French abortion pill to women in this country has encountered yet another obstacle: a suggestion by the Food and Drug Administration that it may place tight restrictions on how the drug, RU-486, is distributed and who can prescribe it.

Typically, once a drug is approved, any doctor can prescribe it for any purpose. But people familiar with negotiations between the F.D.A. and the sponsor of RU-486, which is also known as mifepristone, say the agency is considering taking several unusual steps, including restricting prescribing privileges to doctors who perform surgical abortions.

That would effectively eliminate what advocates of abortion rights see as mifepristone's main advantage, moving the procedure out of potentially high-profile clinics and into the private offices of gynecologists, family practitioners and other doctors.

"It kills the drug if it can't be used by primary care providers," said Dr. Eric Schaff, a professor of family medicine at the University of Rochester who has run clinical trials of RU-486. "The whole idea of mifepristone was to increase access."

Indeed, that is mifepristone's potential. A study released today by the Kaiser Family Foundation found that 1 in 3 gynecologists who do not perform abortions would prescribe mifepristone if it was approved by the F.D.A. But the study also found that doctors would have second thoughts if they were required to undergo training to use the drug, another condition the F.D.A. is considering.

Officials of the food and drug agency refused to comment on the negotiations, as did the Population Council, a nonprofit research group that holds the rights to market mifepristone in the United States.

Heather O'Neill, a spokeswoman for the Danco Group, the investors who have licensed those rights and are arranging for the drug to be manufactured and distributed in this country, said, "The agency's initial approach is more restrictive than we had envisioned for a drug that has been used safely by so many women."

But Ms. O'Neill would not elaborate, beyond saying, "We are in the very early stages of a delicate negotiation process with the F.D.A."

Studies show that when taken with misoprostol, an already approved medication, mifepristone causes abortion -- in essence, a miscarriage -- in more than 95 percent of women who are no more than 49 days pregnant. After years of controversy, the F.D.A. announced in 1996 that mifepristone was safe and

effective for use in this country.

But the final approval process has been fraught with complications, in part because the drug's sponsors had trouble finding a manufacturer. That issue has been settled (the manufacturer's identity remains undisclosed), and in February, the F.D.A. notified the Danco Group that it would give final approval to RU-486 if certain labeling and manufacturing issues could be resolved.

The agency has until Sept. 30 to either approve the drug, reject it or call for a further delay. Negotiations were proceeding apace when, at a Population Council meeting last Friday, officials from the Danco Group announced that they had just received a new set of requirements from the F.D.A. Dr. Michael Burnhill, medical affairs vice president for Planned Parenthood of America, said the list had caught Danco officials by surprise.

"They thought all the F.D.A. requirements had been dropped on the table in February," he said.

In addition to requiring that only abortion practitioners prescribe mifepristone, Dr. Burnhill said, the F.D.A. is demanding that prescribing doctors be trained in mifepristone's use, be trained in reading ultrasound scans, and maintain admitting privileges at hospitals with emergency facilities no more than an hour from their offices, in case women experience complications.

Dr. Burnhill said doctors would have to register with the drug's distributor "so that the distributor would not be supplying the product to every Tom, Dick and Harry." The proposal also contained a subtle, but important, wording change: because the word "physician" was used, not "provider," nurse-practitioners would be unable to prescribe mifepristone.

Though rare, similar requirements have been imposed on other drugs, including thalidomide and certain narcotics used to relieve pain in cancer patients.

Some abortion rights advocates and others who favor approval of RU-486 fear that the requirements would lead to creation of a national list of mifepristone providers, giving abortion opponents an opportunity to single out those doctors. Others say the F.D.A. is succumbing to political pressure and treating women unfairly.

"To encumber a drug like this is extremely unusual for the F.D.A.," said Dr. Wendy Chavkin, a professor of public health at Columbia University. "We have Viagra that went out in widespread fashion even though there was some suggestion that it might cause serious cardiovascular events. In contrast, this is a highly studied drug where the safety and efficacy have been demonstrated. That indicates how the political climate is really interfering in the science."

Organizations mentioned in this article:
Food and Drug Administration

Related Terms:
Abortion; Ru-486 (Drug); Mifepristone (Drug); Doctors

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November 3, 2015

Robert M. Califf, MD, Deputy Commissioner for Medical Products and Tobacco
Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research
Food and Drug Administration
10902 New Hampshire Avenue
Silver Spring, MD 20993

Dear Drs. Califf and Woodcock,

The US Food and Drug Administration approved mifepristone for use in medical abortions on September 28, 2000. Now, 15 years and over 2.5 million uses later, the safety and effectiveness of the drug have been well established by both research and experience, and serious complications have proven to be extremely rare.[1]

We the undersigned are researchers and providers of medical abortion. The organizations we represent include many of the practitioners of medical abortion in the United States. We are writing to present evidence demonstrating that some of the restrictions placed on mifepristone at its initial approval are no longer necessary for the safe and effective use of the drug. We encourage you to exercise your authority to change the label in order to improve both the use of the drug for medical abortion and access to it for this use.

We fully support the following changes to the label:

- The drug should be indicated for use in medical abortions beyond 49 days of gestation.
- The recommended dose regimen should be mifepristone 200 mg followed 24-48 hours later by misoprostol 800 mcg administered buccally.
- The location where the patient should take these drugs should not be restricted.
- An in-person visit should not be mandated for follow-up assessment.
- Any licensed healthcare provider – not just physicians – should be able to prescribe the drug.

All of these provisions are supported by overwhelming evidence and experience, and they reflect current practice in the United States. We hope and expect that you will agree.

We would like to focus here on two additional amendments to the current regulation of mifepristone:

A. Elimination or substantial modification of the Risk Evaluation and Mitigation Strategy (REMS), and
B. Extension of the gestational age limit for medical abortion to 70 days.

Below we discuss the rationale for each of these amendments. Because the elimination or modification of the REMS would have the greatest positive impact on the greatest number of women, we address it first.

A. <u>Elimination or modification of the REMS</u>

When the FDA first approved mifepristone in 2000, experience with its use in non-research settings was minimal, and the decision to impose specific conditions to minimize risk to users was therefore understandable. But over the past 15 years, the safety of the drug has been well established by both research and experience, and serious complications have proven to be extremely rare.[1] Thus, reassessment of the REMS and the Elements To Assure Safe Use (ETASU) which are included in the

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2. Provider certification. The ETASU require that to prescribe mifepristone, a provider must obtain certification by submitting a form attesting that he or she:
   - is able to assess the duration of pregnancy accurately;
   - is able to diagnose ectopic pregnancies;
   - is able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made plans to provide such care through others, and is able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and
   - has read and understood the prescribing information.

   Fulfilling these criteria requires no specialized medical expertise. Although many clinicians use history and/or clinical examination to assess the duration and location of a pregnancy, any provider who is not comfortable with these approaches can order an ultrasound. Similarly, any provider can appropriately plan to provide care for emergencies by referring patients to an emergency room if needed. No licensed healthcare professional would be unable to read or understand the prescribing information. A standard clinical license should be sufficient to assure that a provider meets these qualifications; an exceptional certification for mifepristone is unnecessary.

   Provider certification for mifepristone is also inconsistent with the requirements for prescribing other drugs that require careful patient screening to ensure safety. For example, clinicians are not required to certify their ability to diagnose heart disease before prescribing powerful cardiovascular drugs, to diagnose infections before prescribing antibiotics, or to assess schizophrenia before prescribing antipsychotics. Evaluating a patient for each of these conditions is much more complicated than assessing the duration or location of a pregnancy. Singling out mifepristone for certification is inappropriate.

   Furthermore, the certification process inhibits access to mifepristone. Most immediately, because the certification process must be completed in advance of the patient encounter, it prevents qualified clinicians who have not completed the certification from providing the service to patients who present for care unexpectedly. More broadly, the process of obtaining certification may discourage some providers from offering the service to any patients. Given the history of harassment and violence against abortion providers in this country and the demonstrated difficulty in maintaining confidentiality in the current environment, some clinicians are understandably reluctant to allow their names to be included in a list of abortion providers.

   Finally, the certification requirement should be eliminated because it would be incompatible with standard distribution of mifepristone in pharmacies. Setting up and maintaining a system whereby pharmacies could check the certification status of prescribers would be impractical.

3. Patient Agreement. The requirement that each patient should sign an FDA-approved agreement before receiving mifepristone should also be eliminated. Like the other parts of the ETASU, this requirement is inconsistent with requirements for other drugs with similar or greater risks. Medical abortion is a treatment, not a procedure, and it is highly unusual to require patients to sign agreements for other safe treatments – for example, treatment of a sexually transmitted infection, or a nebulizer treatment for asthma. In addition, in places where off-label use of mifepristone is permitted, the content of any FDA-approved agreement may be inconsistent with the care provided by the individual clinician. The requirement that a patient sign an agreement to a treatment plan that differs from the one offered by her provider is both inappropriate and confusing.

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February 4, 2016

Stephen Ostroff, M.D., Acting Commissioner of Food and Drugs
Robert M. Califf, M.D., Deputy Commissioner for Medical Products and Tobacco
Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Drs. Ostroff, Califf, and Woodcock,

The following 30 organizations write to ask the U.S. Food and Drug Administration (FDA) to lift the Risk Evaluation and Mitigation Strategy (REMS) imposed in 2000 when it approved the use of Mifeprex© (mifepristone) for pregnancy termination, and to extend the indicated use through a gestational age of 70 days. In the 15 years since mifepristone's approval, multiple clinical trials, dozens of studies, and extensive experience across the globe have confirmed the FDA's finding that mifepristone is a safe and reliable method of abortion. Studies have shown that mifepristone in combination with misoprostol is up to 99% effective for first trimester abortion[1,2] and that serious complications are rare.[3] The steady increase in use of medication abortion – now 23% of U.S. abortions – shows that many women prefer this option, and that it has the ability to improve access to abortion, even in states with restrictive laws. Provider interest in offering mifepristone has also increased substantially: in 2011, 59% of abortion providers offered early medication abortions, up from 33% in 2008.[4] This growing use of medication abortion has made a major difference in people's lives. We thank the FDA for ensuring mifepristone is available on the market for patients' reproductive health care needs.

However, many who could benefit from mifepristone still do not have access to it due to multiple types of restrictions, including those required by the FDA. In November 2015, a group of organizational and individual researchers submitted a letter to the FDA (hereinafter "Technical Letter") asking the agency to lift the REMS on mifepristone and extend the indicated use to 70 days gestational age, presenting data showing that the current restrictions and limited gestational age indication are unnecessary for the safe and effective use of the drug for pregnancy termination.

As policy, advocacy, social science, research, and academic organizations, we ask the FDA to consider the substantial evidence presented in the Technical Letter, alongside the burdens that the REMS and the label's 49-day gestational age indication place on patient access, which we describe here. The FDA held a public meeting in October 2015 to discuss improving patient access to drugs under REMS,[5] evidencing the agency's own awareness of patient burden caused specifically by restrictions imposed under REMS. We applaud these efforts and urge the FDA to use its regulatory authority to remove the medically unnecessary barriers to mifepristone.

Mifepristone underwent a lengthy approval process in the late 1990s, during which it became subject to a rarely-used approval mechanism: Subpart H of the FDA's Title 21, Chapter 314 regulations. Subpart H is used primarily for drugs with very serious and well-documented safety concerns.[6] In 2007, Subpart H restrictions on all drugs were converted automatically into a Risk Evaluation and Management Strategy (REMS),[7] a mechanism created by Congress whereby FDA can impose Elements to Assure Safe Use (ETASU). Under this law, as the Agency stated in preparation for its October 2015 meeting on REMS,[8] Congress mandated that the FDA engage in a balancing analysis to ensure that the risks mitigated by a REMS program do not unduly burden patients' access to health care:

disproportionately people of color.[12] Costly and unnecessary visits to the doctor significantly increase financial and logistical burdens for these individuals and communities.

Any venue expansion, however, should not preclude the direct distribution of mifepristone to providers who want to dispense from their clinical settings. In many places, pharmacy refusal laws allow pharmacists to decline to fill prescriptions for reproductive health drugs such as emergency contraception and birth control, and federal policy allows providers to refuse to provide abortions.[13] So, although pharmacists' ability to dispense mifepristone would expand patient access to medication abortion in places where providers cannot easily store mifepristone in their offices, providers should retain the option to have mifepristone directly distributed to their offices to ensure continued access to medication abortion for those living in places where pharmacists can refuse to fill mifepristone prescriptions.

b. **Eliminate the Prescriber Agreement certification requirement.** Under the REMS and ETASU, providers must have a physician supervisor submit a Prescriber Agreement form to the drug's distributor attesting: 1) that mifepristone will only be provided by or under the supervision of a physician; and 2) that the physician can assess pregnancy duration, 3) diagnose ectopic pregnancies, and 4) make a plan for a patient to have surgical intervention if necessary.[10] This requirement should be eliminated for several reasons:

i. *The Prescriber's Agreement is unnecessary for the safe dispensation of mifepristone.* As the Technical Letter explains, health care professionals are already subject to many laws, policies, and ordinary standards of practice that ensure they can accurately and safely understand and prescribe medications. Provider certification is not required for health care professionals to dispense other drugs, including drugs that carry black box, or boxed, warnings about their medical risks. Accutane, for example, has a boxed warning that describes the potential risks of the drug,[14] but Accutane prescribers are not required to submit a certification form in order to prescribe it. Mifeprex also has a boxed warning[15] and there is no medical reason for a Prescriber's Agreement to be required in addition.

ii. *The Prescriber's Agreement forces providers to identify themselves as abortion providers to a centralized entity (Danco Laboratories) inspected and regulated by the FDA, which could discourage some from offering medication abortion care to their patients*. In 2014, more than half of U.S. health care facilities that provide abortions (52%) experienced threats and other types of targeted intimidation, and one in five experienced severe violence, such as blockades, invasions, bombings, arsons, chemical attacks, physical violence, stalking, gunfire, bomb threats, arson threats, or death threats.[16] Robert Dear's November 27, 2015, standoff at a Planned Parenthood health center in Colorado, which resulted in three deaths, provides one recent and chilling example of anti-abortion violence.[17] Given such escalating harassment and violence against known abortion providers,[18] clinicians may be understandably reluctant to add their names to a centralized database of mifepristone providers.

iii. *The Prescriber's Agreement would be incompatible and unnecessary if there were an expanded distribution system.* If dispensing venues are expanded as proposed in section 1a, ordinary standards of practice and state regulations would govern pharmacists' and providers' distribution of mifepristone, and a specific certification process would be unnecessary. Furthermore, a distribution system that incorporates the Prescriber's Agreement would be extremely difficult to maintain as a practical matter. Pharmacists would need to check the certification status of each prescriber before filling a prescription, which they do not normally have to do when filling other prescriptions.

Alternatively, pharmacists would need to become certified providers themselves, thus facing the deterrence problem of adding their names to a centralized database of mifepristone providers.

iv. *The Prescriber's Agreement as currently written prevents independent non-physician prescribers from being able to prescribe mifepristone without supervision by a physician.* The Prescriber's Agreement currently states that mifepristone "must be provided by or under the supervision of a physician."[19] However, nowhere in the outline piece of the REMS document written by the FDA is the word "physician" used. The REMS references only "providers" and "prescribers." [10] The Prescriber's Agreement's narrow interpretation of the REMS is medically unnecessary and severely limits patients' access to medication abortion care, because non-physician providers must work under physician supervision to prescribe mifepristone. All states give certain advanced practice clinicians prescribing authority, including for controlled substances, and 27 states allow them to dispense medications directly.[20] Advanced practice clinicians provide an increasing proportion of basic health care in the U.S., and several states authorize these clinicians to provide abortion care. If the Agreement is not eliminated, then at least enlarging the pool of health care providers that can submit the Prescriber's Agreement would help improve access and be consistent with individual state law regarding scope of practice. If the FDA does not eliminate the Agreement altogether, it should make clear that any licensed health care provider with prescribing authority is also eligible for certification to prescribe mifepristone.

c. **Remove the confusing and unnecessary Patient Agreement.** The REMS requires that each patient sign a Patient Agreement form before receiving mifepristone. This requirement is medically unnecessary and interferes with the clinician-patient relationship. It should be eliminated entirely.

In addition to being outdated and inconsistent with requirements for drugs with similar safety profiles, the Patient Agreement creates confusion for patients. Except in the few states that require that patients follow the regimen that appears on the mifepristone label, the majority of clinicians use an evidence-based regimen that is different from the regimen described in the label. Requiring a patient to sign an agreement to a treatment plan that differs from the one prescribed by her provider is confusing and could undermine trust in the clinician.

Patients have been using mifepristone safely and effectively according to evidence-based regimens recommended by their clinicians for many years, diverging from the regimen described in the Patient Agreement.[3] A wealth of data and experience since mifepristone's approval have demonstrated that this drug is extremely safe, that clinicians with routine professional training can provide it appropriately, and that patients are able to use it as directed by their health care provider.[21,22] Requiring a patient to sign an agreement to a treatment plan that differs from the one prescribed by her provider may create unnecessary confusion.

d. **Allow evidence-based follow-up assessment.** Under the Federal Food, Drug, and Cosmetic Act, the FDA should ensure that a REMS does not unduly burden patients, especially those in rural or medically underserved areas.[9] However, the documents appended to the REMS (the Medication Guide, Prescriber's Agreement, and Patient Agreement) all indicate the patient should to return to the clinic for follow-up 14 days after the patient takes mifepristone.[10] Such an in-person appointment is not always medically necessary and, when required, creates significant additional costs for patients, who must find time for another appointment at the provider's office and potentially incur substantial costs for travel, childcare, and/or lost wages.

ACOG
THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

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November 4, 2015

Robert M. Califf, MD, Deputy Commissioner for Medical Products and Tobacco
Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research
Food and Drug Administration
10902 New Hampshire Avenue
Silver Spring, MD 20993

Dear Drs. Califf and Woodcock:

On behalf of the American Congress of Obstetricians and Gynecologists (ACOG), an organization representing 58,000 physicians and partners in women's health, I would like to present our recommendations regarding the safety, effectiveness, and use of mifepristone. We hope this information will be useful to FDA in any future deliberations regarding revisions to the drug label, Risk Evaluation and Mitigation Strategy (REMS), and Elements To Assure Safe Use (ETASU).

Since FDA approval in 2000, mifepristone has been used by women over 2.5 million times as a safe, effective method of pregnancy termination. As outlined in the enclosed Committee Opinion #613, ACOG supports access to safe, legal abortion services as a necessary component of women's health care, supports the availability of high-quality reproductive health services for all women, and is committed to improving access to abortion. As our knowledge regarding mifepristone advances, we believe its labeling, REMS, and ETASU have become outdated and have limited women's access to safe, effective abortion care.

ACOG supports evidence-based regimens for provision of medication abortion services, as outlined in the enclosed Practice Bulletin #143. These evidence-based regimens have improved medication abortion in terms of expense, safety, speed, and adverse effects. Based on efficacy and the adverse effect profile, evidence-based protocols for medication abortion are superior to the FDA-approved regimen.

Regimens that use low doses of mifepristone (200 mg) have similar efficacy and lower costs compared with those that use mifepristone at 600 mg. Vaginal, buccal, and sublingual routes of misoprostol administration increase efficacy, decrease continuing pregnancy rates, and increase the gestational age range for use as compared with the FDA-approved regimen. ACOG supports efforts to align FDA labeling for mifepristone with evidence-based regimens.

In addition, ACOG would fully support the following changes to the current label, consistent with ACOG recommendations outlined in Practice Bulletin #143:

1. The drug should be indicated for use in medical abortions up to 70 days of gestation

   Although the method is most commonly used up to 63 days of gestation, the treatment is also effective after 63 days gestation[i].

2. The location where the patient should take these drugs should not be restricted

   There is no clinical justification for restrictions or regulations regarding the location of mifepristone or misoprostol ingestion or administration.

3. An in-person visit should not be mandated for follow-up assessment

   Follow-up after medication abortion is important, although an in-clinic evaluation is not always necessary.

4. Any licensed healthcare provider should be able to prescribe the drug, not just physicians

   Medication abortion can be provided safely and effectively by nonphysician clinicians.

In addition to the above recommendations, ACOG finds evidence regarding the safety of the drug over the past 15 years of use in the United States to be a compelling argument for the removal or substantial modification of the Risk Evaluation and Mitigation Strategy (REMS) and Elements to Assure Safe Use (ETASU) for mifepristone[ii]. These requirements are inconsistent with requirements for other drugs with similar or greater risks and serve as barriers to access without demonstrated improvements to patient safety or outcomes. Prescription access to medication abortion has been shown to improve access to care, and could also facilitate expansion of telemedicine models of provision that have been shown to increase access, particularly for women in rural areas.[iii] [iv] [v]

ACOG opposes regulations or restrictions that are inappropriately unique to the provision of abortion and that mandate procedures and care that are not evidence-based. The safety record of this drug does not warrant restrictions such as provider certification, dispensing of the drug in specific locations, or specified patient consent. A standard clinical license should be sufficient to ensure that a practitioner meets qualifications for prescribing mifepristone. Mandating the location where the drug is to be dispensed has no bearing on risk. The requirement that patients sign an FDA-approved agreement before receiving mifepristone is inconsistent with requirements for other drugs with similar or greater risks. In line with its safety record and to improve access, we recommend that mifepristone be made available in retail pharmacies like other prescription drugs, without unique provider certification or patient consent requirements.

Thank you for your consideration. We are available to answer any questions you may have regarding these issues.

Sincerely,

Hal C Lawrence MD

Hal C. Lawrence, III, MD, FACOG
Executive Vice President and CEO

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