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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAII

GRAHAM T. CHELIUS, M.D., *et al.*, Plaintiffs, vs. ALEX M. AZAR, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*, Defendants.	CIV. NO. 1:17-cv-00493-JAO-RT **JOINT STIPULATION OF FACTS**

JOINT STIPULATION OF FACTS

Solely for purposes of resolution of the Cross-Motions for Summary Judgment, the Parties stipulate to each of the following facts:

FDA Regulatory Background

1. Before a new drug can be marketed in the United States, the drug sponsor must submit a new drug application ("NDA") to the U.S. Food and Drug Administration ("FDA").
2. According to the FDA website, "FDA approval of a drug means that data on the drug's effects have been reviewed by the [FDA's] Center for Drug Evaluation and Research, and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population. The drug approval process takes place within a structured framework that includes:
    - ***Analysis of the target condition and available treatments***—FDA reviewers analyze the condition or illness for which the drug is intended and evaluate the current treatment landscape, which provide the context for weighing the drug's risks and benefits. For example, a drug intended to treat patients with a life-threatening disease for which no other therapy exists may be considered to have benefits that outweigh the risks even if those risks would be considered unacceptable for a condition that is not life threatening.

- ***Assessment of benefits and risks from clinical data***—FDA reviewers evaluate clinical benefit and risk information submitted by the drug maker, taking into account any uncertainties that may result from imperfect or incomplete data. Generally, the agency expects that the drug maker will submit results from two well-designed clinical trials, to be sure that the findings from the first trial are not the result of chance or bias. In certain cases, especially if the disease is rare and multiple trials may not be feasible, convincing evidence from one clinical trial may be enough. Evidence that the drug will benefit the target population should outweigh any risks and uncertainties.
- ***Strategies for managing risks***—All drugs have risks. Risk management strategies include an FDA-approved drug label, which clearly describes the drug's benefits and risks, and how the risks can be detected and managed. Sometimes, more effort is needed to manage risks. In these cases, a drug maker may need to implement a Risk [Evaluation] and Mitigation Strategy (REMS)."

3. A drug sponsor may request changes to a previously approved NDA by submitting to the FDA a supplemental NDA ("SNDA").
4. The FDA follows a similar process in evaluating an SNDA as it does in evaluating an NDA.

5. Every NDA holder is required to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience reports.
6. FDA routinely monitors post-marketing safety data (including 15-day safety reports, individual case safety reports, and periodic adverse drug experience reports) for all approved drugs.

Mifeprex Regulatory Background

7. Mifepristone was approved for the medical termination of early pregnancy in France and China in 1988; in the United Kingdom in 1991; and in other European countries throughout the 1990s.
8. In March 1996, the Population Council, a nonprofit organization based in the United States, sponsored an NDA for Mifeprex for use in combination with misoprostol for the medical termination of early pregnancy.
9. In 1999, the Population Council contracted with Danco Laboratories, L.L.C. ("Danco") for the manufacturing and marketing of Mifeprex.
10. On September 28, 2000, the FDA approved mifepristone under the brand name Mifeprex® for use, in a regimen with the drug misoprostol, as a medical option for terminating an early pregnancy.
11. Danco began distribution of Mifeprex in November 2000.

12. The Population Council subsequently transferred ownership of the Mifeprex NDA to Danco.

13. Mifeprex is a single tablet that is only prescribed for a single use.

14. The FDA originally authorized Mifeprex for use in a 600-mg dose, in a regimen with misoprostol, to terminate an intrauterine pregnancy through 49 days of pregnancy.

15. Since 2016, Mifeprex has been approved for use in a 200-mg dose, in a regimen with misoprostol, to terminate an intrauterine pregnancy through 70 days of pregnancy.

16. Prior to 2016, the Mifeprex *Patient Agreement Form* included the following statements: "I understand that I will take Mifeprex in my provider's office (Day 1)." and "I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3)."

17. A true and correct copy of the current Mifeprex labeling is attached as **Exhibit A**.

18. Since 2016, the Mifeprex label has provided the following dosing regimen:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
    - Day One: MIFEPREX Administration

      One 200 mg tablet of MIFEPREX is taken in a single oral dose.

- Day Two or Three: Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)

  Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

19. The Black Box warning on the current Mifeprex label states in full:

"WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established. Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., Clostridium sordellii) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis [see Warnings and Precautions (5.1)]. Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical

attention if they experience prolonged heavy vaginal bleeding [see Warnings and Precautions (5.2)]. Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program [see Warnings and Precautions (5.3)]. Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol. Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion."

20. There is no known risk of a patient developing a dependency on Mifeprex.

21. As of March 2016, approximately 2.5 million women in the U.S. had used Mifeprex. As of December 2017, more than 3 million women in the U.S. had used Mifeprex.

22. The FDA originally approved Mifeprex under its "Subpart H" regulations (21 C.F.R. §§ 314.500-560) and subject to certain restrictions.

23. In 2007, pursuant to Section 909(b)(1) of the newly enacted Food and Drug Administration Amendments Act of 2007, Mifeprex was "deemed to have in effect an approved risk evaluation and mitigation strategy" (*i.e.*, REMS) because the FDA previously had approved it with certain restrictions under its "Subpart H" regulations.

24. In 2011, the FDA affirmatively approved Mifeprex's REMS, maintaining the same requirements initially imposed in 2000 and subsequently deemed a REMS in 2007. A true and correct copy of the Mifeprex REMS approved in 2011 is attached as **Exhibit B**.

25. In 2015, Danco submitted an SNDA seeking approval to alter the Mifeprex indication, labeling, and REMS to reflect an updated, evidence-based prescription regimen.

26. The FDA reviewed both the Mifeprex label and REMS in 2015-2016.

27. In 2016, the FDA reauthorized the Mifeprex REMS. A true and correct copy of the Mifeprex REMS approved in March 2016 is attached as **Exhibit C**.

28. The Mifeprex REMS includes three Elements to Assure Safe Usage ("ETASU"):

- **The Prescriber Certification Requirement** (ETASU A) provides that health care providers who prescribe Mifeprex must be specially certified. To become specially certified, a health care provider must review the Prescribing Information for Mifeprex; complete the *Prescriber Agreement Form*; and follow certain guidelines for use of Mifeprex. By signing the *Prescriber Agreement Form*, prescribers agree that they have the ability to assess the duration of pregnancy accurately, the ability to diagnose ectopic pregnancies, and the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; prescribers also agree that they will follow the guidelines for use of Mifeprex. The guidelines for use of Mifeprex require prescribers to review the *Patient Agreement Form* with the patient; fully explain the risks of the Mifeprex treatment regimen; answer any questions the patient may have prior to receiving Mifeprex; sign the *Patient Agreement Form* and obtain the Patient's signature on the *Form*; provide the patient with a copy of the *Patient Agreement Form* and the Mifeprex Medication Guide; place the signed *Patient Agreement Form* in the patient's medical record; record the serial number from each

package of Mifeprex in each patient's record; and report any deaths to Danco, identifying the patient by a non-identifiable reference and the serial number from each package of Mifeprex. Danco is responsible for ensuring that healthcare providers who prescribe Mifeprex are specially certified in accordance with these requirements and de-certifying health care providers who do not maintain compliance with certification requirements. Danco is also required to provide the prescribing information and *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

- **The Restricted Distribution Requirement** (ETASU C), provides that Mifeprex must be dispensed to patients only in certain health care settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber; and that Danco must ensure that Mifeprex is not distributed to or dispensed through retail pharmacies, mail-order pharmacies, or any other setting not described above.
- **The Patient Agreement Requirement** (ETASU D), provides that a patient must sign a *Patient Agreement Form* indicating that she has received, read, and been provided a copy of the *Patient Agreement Form*, and received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

29. The REMS does not require that the patient take Mifeprex in certain health care settings, only that it be dispensed to her in certain health care settings. The patient may self-administer the medication in a location of her choosing, outside a supervised setting.

30. The *Patient Agreement Form* approved in 2016 includes the following statement: "I understand:

    a. I will take Mifeprex on Day 1.

    b. My provider will either give me or prescribe for me the misoprostol tablets which I will take 24 to 48 hours after I take Mifeprex."

31. Between November 2015 and February 2016, the FDA received three letters from representatives of academia and various professional organizations relating to the Mifeprex SNDA and REMS ("the Letters").

32. The first letter was dated November 3, 2015, and signed by the American Public Health Association (Population, Reproductive, and Sexual Health Section); Gynuity Health Projects; Ibis Reproductive Health; the National Abortion Federation; and clinicians from the Albert Einstein College of Medicine, Columbia University, Princeton University, Stanford University, the University of California San Francisco, the University of North Carolina,

the University of New Mexico, and the University of Ottawa, among others. A true and correct copy is attached as **Exhibit D**.

33. The second letter was dated November 4, 2015, and signed by Hal C. Lawrence, III, MD, FACOB, the Executive Vice President and CEO of the American College of Obstetricians and Gynecologists. A true and correct copy is attached as **Exhibit E**.

34. The third letter was dated February 4, 2016, and signed by the Association of Reproductive Health Professionals, Ibis Reproductive Health, Gynuity Health Projects, the National Abortion Federation, Planned Parenthood Federation of America, and the Society of Family Planning, among others. A true and correct copy is attached as **Exhibit F**.

35. The Letters requested certain changes to the Mifeprex labeling, and that the REMS be modified or eliminated, to remove the Patient Agreement and eliminate the prescriber certification, while allowing Mifeprex to be dispensed through retail pharmacies.

36. In a February 25, 2016, letter addressed to the principal signatory of the third Advocacy Group Letter, Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research ("CDER"), wrote: "Thank you for your letter dated February 4, 2016, to [then-Acting FDA Commissioner] Dr. Ostroff, Dr. Califf, and me with recommendations to lift the Risk Evaluation and

Mitigation Strategy (REMS) for Mifeprex (mifepristone), and to extend the indicated use of Mifeprex through a gestational age of 70 days. Dr. Ostroff has asked me to respond on behalf of the FDA because the Center for Drug Evaluation and Research is responsible for regulating all drugs, including mifepristone. Please share this response with your cosigners. In your letter, you strongly encouraged FDA to revise the mifepristone label and eliminate the REMS restrictions, especially the Elements to Assure Safe Use, which includes the prescriber and patient agreements. You requested that the dose regimen be changed to mifepristone 200 mg followed 24-48 hours later by misoprostol 800 mcg. You also recommended not restricting the location where the patient should take these drugs and stated that an in-person visit is not always necessary for a follow-up assessment. Moreover, you proposed that any licensed health care provider should be able to prescribe mifepristone, and that it be available through pharmacies as well as provider offices. Your letter has been shared with the appropriate FDA staff and will be carefully reviewed." A true and correct copy of that letter is attached as **Exhibit G**.

37. As part of their consideration of whether each element of the Mifeprex REMS continued to be necessary to ensure that the benefits of Mifeprex outweigh its risks for the approved indication, 11 FDA employees (eight

managers and three reviewers/analysts) recommended that the Patient Agreement Form be removed from the Mifeprex REMS.

38. Dr. Robert M. Califf, the former Commissioner of Food and Drugs ("Commissioner"), was briefed orally on March 2 and/or 18, 2016, about the Mifeprex SNDA, including the conclusion of the FDA's CDER that a REMS remained necessary to ensure that the benefits of Mifeprex outweigh its risks, but that the REMS should be modified, including by removing one component of the REMS, the Patient Agreement Form.

39. The Commissioner is a political appointee.

40. Subsequent to being briefed, the Commissioner requested that the Patient Agreement Form remain a component of the Mifeprex REMS.

41. In a March 28, 2016, memorandum documenting the Commissioner's request and related action, Dr. Woodcock wrote: "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 [the SNDA submitted by Danco], [**redacted**] 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 [for Drug Evaluation and Research] 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 [**redacted**] and [**redacted**] to continue to include a Patient Agreement Form in the REMS for Mifeprex."

42. The Mifeprex REMS approved in 2016 contains the same restrictions that were originally imposed in 2000 pursuant to FDA's Subpart H regulations; then deemed a REMS in 2007; and then affirmatively approved in 2011, with three changes: (1) Revisions to the Prescriber Agreement Form; (2) Removal of the Medication Guide as a REMS Element; and (3) Updating of the REMS Goals to reflect the above changes.

43. The 2016 REMS also removed the requirement that Danco report to the FDA certain specifically enumerated adverse events, such as all

hospitalizations due to complications or blood transfusions, but retained the reporting requirement as to deaths.

44. In addition to Dr. Califf, other politically-appointed FDA employees in the Office of the Commissioner were involved in the 2016 Mifeprex REMS decision.

45. The following materials were presented to politically-appointed FDA employees in relation to the 2016 decision that a REMS remained necessary to ensure the safe use of Mifeprex: A high-level summary of the history of Mifeprex and the pending SNDA, including potential modifications to the REMS; the Advocacy Group Letters; drafts of potential responses to press inquiries; drafts of material to be posted on FDA's website regarding Mifeprex; and a draft of the SNDA approval.

46. In April 2019, the FDA approved a generic version of mifepristone for use as a medical option of terminating an early pregnancy. It has the same labeling as Mifeprex and is required to use the single, shared system REMS with Mifeprex.

47. In a declaration dated October 8, 2019, Janet Woodcock, the Director of the FDA's CDER, stated: "In light of the violence and harassment surrounding the provision of abortion, FDA withheld FDA employee names and other identifying information from documents related to Mifeprex in the

administrative record produced in this case due to the risk to the health and/or safety of those employees if their names and/or identifying information were made public. Since 2000, FDA has withheld this information from agency records related to Mifeprex because of these risks. Because releasing this information would constitute an unwarranted invasion of personal privacy and could expose those employees to threats, intimidation, harassment and/or violence, FDA believes it is necessary not to disclose information that could be used to identify these employees to any person outside of FDA, including Plaintiffs' counsel subject to a protective order."

Mifeprex REMS Goals and Rationales

48. Prior to March 2016, the official Mifeprex REMS Goals were:

- "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."

49. As of March 2016, the official Mifeprex REMS Goal 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.

b) Ensuring that Mifeprex is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber.

c) Informing patients about the risk of serious complications associated with Mifeprex."

50. There are two documents in the Administrative Record that set out the FDA's rationale for maintaining the Mifeprex REMS: First, an October 2013 memorandum entitled *Final Risk Evaluation and Mitigation Strategy (REMS) Review* for Mifeprex (the "2013 REMS Review"), a true and correct copy of which is attached as **Exhibit H**. Second, a March 2016 memorandum entitled *Risk Assessment and Risk Mitigation Review(s)* for Mifeprex ("2016 REMS Review"), a true and correct copy of which is attached as **Exhibit I**.

51. The 2013 REMS Review includes a section entitled "Impact of REMS Elements and Their Removal," with subsections on "Prescriber Certification" (*i.e.*, ETASU A); "Restricted to Certain Healthcare Settings" (*i.e.*, ETASU C); and "Documentation of Safe Use Conditions," (*i.e.*, ETASU D).

52. The "Prescriber Certification"/ETASU A subsection of the 2013 REMS Review states in full: "This Prescriber Agreement is a one-time event with limited burden. Prescriber certification probably has the most influence of the three ETASUs in addressing safe use and limiting access to Mifeprex because this element requires physicians to attest to having certain skills, agree to abide by the program requirements including reporting of serious adverse events, and complete an additional step (e.g., the enrollment form) in the usual drug procurement process. Eliminating this element opens access to any prescriber. Therefore, it is possible that physicians and advanced practice healthcare providers (e.g., physician assistants, nurse practitioners) who are not familiar with Mifeprex and/or practice outside of facilities with established protocols may prescribe Mifeprex; a factor that could contribute to an increase in serious complications."

53. The "Restricted to Certain Healthcare Settings"/ETASU C subsection of the 2013 REMS Review states in full: "This element limits distribution by preventing the distribution of Mifeprex through retail (including mail order and internet) pharmacies. If this restriction was removed, any pharmacy could stock the drug and prescribers would no longer have to stock Mifeprex. In a 'worst case' scenario, the following *could* occur:

- patients are not properly counseled about the serious complications and what to do in the event that they experience an adverse event,

- patients may not pick-up the prescription – failing to initiate the abortion in a timely manner resulting in ineffective or inappropriate use of the drug or potentially an increased incidence of complications,

- patients have difficulty finding a pharmacy that stocks the drug because not all pharmacies may choose to stock the drug, resulting in treatment delay.

Although not safety concerns, confidentiality and personal safety are significant concerns with Mifeprex. Distribution through retail pharmacies could compromise patient and prescriber confidentiality with adding a new stakeholder to the treatment process, and pharmacies could be targeted by individuals or groups opposed to abortions. Restriction of mifepristone to certain healthcare settings is probably the most critical element for maintaining confidentiality and privacy for both patients and prescribers. This element also contributes to the patient's safe use of Mifeprex by making the prescriber responsible for giving the drug directly to the patient and counseling the patient at the time of dispensing. It is safer for the patient - providing the opportunity for direct observed therapy (although this is not a REMS program requirement) to initiate the time-sensitive abortion process, and ensures the patient leaves the healthcare facility with the medications that are necessary for completing a medical abortion to maximize efficacy and minimize risk."

54. The "Documentation of Safe Use Conditions"/ ETASU D subsection of the 2013 REMS Review states in full: "The REMS requires that prescribers review and complete a Patient Agreement with each patient before treatment is initiated. The signed Agreement is placed in the patient's medical record; however it is not collected by Danco. There is no data available on how often the Agreement is utilized. Family planning clinics generally utilize consent forms and in this type of practice setting the Patient Agreement may be redundant. Therefore, it is not known if removing this element would increase the risk that a patient is not properly informed and counseled about complications and what to do when a complication occurs."

55. The 2013 REMS Review includes a section entitled "Discussion," which states in full: "[**redacted**] and [**redacted**] considered two options – maintain the REMS or eliminate the REMS with the following possible rationale for each option:

- Eliminate the REMS: No new safety concerns have been identified in 6-7 years. The serious complications being reported now have been consistent with labeling and the reporting rate has been stable over the last several years. These complications are consistent with what one would expect with a surgical abortion and are not necessarily unique to a medical abortion with Mifeprex. Use of Mifeprex has been

primarily in Planned Parenthood and other family planning clinics where there are protocols and familiarity with assessing the duration of pregnancy, diagnosing an ectopic pregnancy, performing surgical interventions in cases of incomplete abortion, and caring for patients that experience serious complications. Some of the safe use practices surrounding Mifeprex may therefore already be embedded in these practice sites that already [sic] dispensing Mifeprex and would likely be maintained even if the REMS were eliminated.

- Maintain the REMS: There have been a small number of reported serious complications associated with Mifeprex and this is likely reflective of the use of Mifeprex within a system of knowledgeable healthcare providers, safe use protocols, proper patient counseling, and follow-up procedures. Medical abortion accounts for the minority of abortions in the U.S. Similarly, training opportunities in medical abortion appear limited and are less available than surgical abortion experience. Given this relative lack of familiarity and experience with medical abortion, a restricted distribution program that reinforces the necessary skills and appropriate care (i.e., counseling and follow-up) is necessary to assure safe use of Mifeprex. The Mifeprex REMS provides the foundation to ensure the implementation of safe use

> conditions with Mifeprex use. Accurate gestation date, patient education, dispensing Mifeprex directly to the patient during the office visit, and timely access to medical care remain important to maintaining the current safety profile of Mifeprex. It is not likely that the essential safe use conditions will be maintained to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events."

56. The 2013 REMS Review includes a section entitled "Recommendation and Conclusion," which states in full: "[**Redacted**] recommends that the existing elements of the REMS should be maintained. Specifically, prescriber certification and dispensing limited to certain healthcare setting provide a framework to ensure that the benefits of Mifeprex outweigh its risks in an appropriate patient population. On January 30, 2013, [redacted] and [redacted] presented this recommendation to the Center Director and senior level management from [redacted]. There was general consensus that a REMS is necessary to ensure that the benefits outweigh its risks."

57. The March 2016 REMS Review states in part: "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. 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."

Other Stipulations

58. There are over 20,000 prescription drug products that are FDA-approved for marketing.

59. As of November 8, 2019, the FDA subjects 530 drug applications to a REMS, 75% of which are opioids.

60. As of November 8, 2019, the FDA subjects 15 drug applications—two of which are Mifeprex and its approved generic—to a REMS that requires that the drug product be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

61. Misoprostol is not subject to a REMS and may be obtained by prescription from a pharmacy.

62. Korlym® (mifepristone) tablets, 300 mg., is FDA-approved 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 in whom surgery has not been successful or who are not candidates for surgery.

63. Korlym was initially approved on February 17, 2012.

64. Korlym is approved for chronic, daily use in doses ranging from 300 to 1200 mg.

65. Korlym is not subject to a REMS. It is available through a specialty pharmacy pursuant to a voluntary restricted distribution system.

66. At least eight FDA managers and two reviewers/analysts were involved in both the 2016 determination that a REMS continues to be necessary to ensure the safe use of Mifeprex, and the decision not to impose a REMS for Korlym.

67. Any provider who is not comfortable using patient medical history or a clinical examination to assess the duration and location of a pregnancy can obtain that information by ordering an ultrasound.

Dated: November 27, 2019

Respectfully submitted,

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Exhibit A

Mifeprex Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning.

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- **Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)**

MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program (5.3).
Before prescribing MIFEPREX, inform the patient about these risks.
Ensure the patient knows whom to call and what to do if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.
Advise the patient to take the MEDICATION GUIDE with her if she visits an emergency room or another healthcare provider who did not prescribe MIFEPREX, so that provider knows that she is undergoing a medical abortion. (5.1, 5.2)

----------RECENT MAJOR CHANGES----------

Boxed Warning	3/2016
Indications and Usage (1)	3/2016
Dosage and Administration, Dosing Regimen (2.1)	3/2016
Dosage and Administration, Post-treatment Assessment: Day 7 to 14 (2.3)	3/2016
Warnings and Precautions, MIFEPREX REMS Program (5.3)	3/2016
Warnings and Precautions, Ectopic Pregnancy (5.4)	3/2016

----------INDICATIONS AND USAGE----------

MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

----------DOSAGE AND ADMINISTRATION----------

- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

----------CONTRAINDICATIONS----------

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

----------WARNINGS AND PRECAUTIONS----------

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or www.earlyoptionpill.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 3/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis *[see Warnings and Precautions (5.1)]*.**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding *[see Warnings and Precautions (5.2)]*.**

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program *[see Warnings and Precautions (5.3)]*.

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.

Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

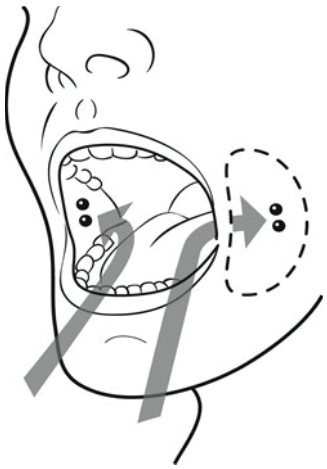
Remove any intrauterine device ("IUD") before treatment with MIFEPREX begins [*see Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
  - *Day One:* MIFEPREX Administration
    One 200 mg tablet of MIFEPREX is taken in a single oral dose.
  - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)
    Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

    Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

    Figure 1



    2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol *[see Clinical Studies (14)]*, discuss with the patient an appropriate location for her to be when she takes the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms *[see Adverse Reactions (6)].*

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if she has questions following the administration of the misoprostol

- The name and phone number of the healthcare provider who will be handling emergencies.

2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, women may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took Mifeprex and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Women who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion *[see Use in Specific Populations (8.1)]*. Advise the patient whether you will provide such care or will refer her to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with “MF.”

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the “treatment procedure”) is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) *[see Warnings and Precautions (5.4)]*
  - Chronic adrenal failure (risk of acute renal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute renal insufficiency)

- History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported *[see Adverse Reactions (6.2)]*)
- Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)
- Inherited porphyrias (risk of worsening or of precipitation of attacks)

- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device ("IUD") in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX *[see Boxed Warning]*. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion *[see Boxed Warning]*.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring

surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

5.3 MIFEPREX REMS Program

MIFEPREX is available only through a restricted program under a REMS called the MIFEPREX REMS Program, because of the risks of serious complications *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the MIFEPREX REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form
- Patients must sign a Patient Agreement Form.
- MIFEPREX must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices and hospitals by or under the supervision of a certified prescriber

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies *[see Contraindications (4)]*. 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.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis *[see Warnings and Precautions (5.1)]*
- Uterine bleeding *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from US studies, because rates reported in non-US studies were markedly lower and are not likely generalizable to the US population. In three US clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label.

Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most women can expect bleeding more heavily than they do during a heavy menstrual period *[see Warnings and Precautions (5.2)]*.

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# US studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-US Clinical Studies

Adverse Reaction	US			Non-US		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported
* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)
Blood and the lymphatic system disorders: anemia
Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)
Psychiatric disorders: anxiety
Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)
Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness
Respiratory, thoracic and mediastinal disorders: shortness of breath
Gastrointestinal disorders: dyspepsia
Musculoskeletal, connective tissue and bone disorders: back pain, leg pain
Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea
General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

regimen is unknown. Refer to the follow-up assessment *[see Dosage and Administration (2.3)]* to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Mifepristone is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant women are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant women with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone,fetal losses were much higher than in control animals. Skull deformaties were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

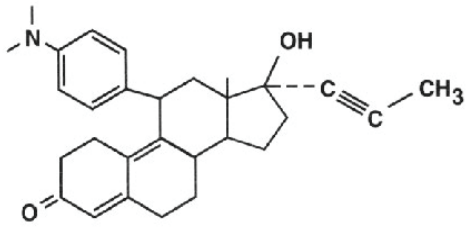
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for Cmax after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in women of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean Cmax was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean $AUC_{0-\infty}$ was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal) Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%

* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.
** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	<49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program *[see Warnings and Precautions (5.3)].*

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with “MF.” Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [see Warnings and Precautions (5.2)].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [see Warnings and Precautions (5.1, 5.2)].
- MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program [see Warnings and Precautions (5.3)]. Under the Mifeprex REMS Program:
    - Patients must sign a Patient Agreement Form.
    - MIFEPREX is only available in clinics, medical offices and hospitals and not through retail pharmacies.

Provider Contacts and Actions in Case of Complications

- Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if she experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever *[see Boxed Warning]*.
- Advise the patient to take the Medication Guide with her if she visits an emergency room or another healthcare provider who did not prescribe MIFEPREX, so that provider will be aware that the patient is undergoing a medical abortion with MIFEPREX.

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to14 days after taking MIFEPREX *[see Dosage and Administration (2.3)]*.
- Explain that
    - prolonged heavy vaginal bleeding is not proof of a complete abortion,
    - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
    - it is recommended that ongoing pregnancy be managed by surgical termination *[see Dosage and Administration (2.3)]*. Advise the patient whether you will provide such care or will refer her to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before she resumes sexual intercourse.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Manufactured for:
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

3/2016

MEDICATION GUIDE

Mifeprex (MIF-eh-prex) (mifepristone) tablets, for oral use

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room. Take this Medication Guide with you. When you visit an emergency room or a healthcare provider who did not give you your Mifeprex, you should give them your Medication Guide so that they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
  Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider in a clinic, medical office, or hospital.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifeprex tablet by mouth.
- Your healthcare provider will either give you or prescribe for you 4 misoprostol tablets to take 24 to 48 hours later.

24 to 48 hours after taking Mifeprex:

- Place 2 misoprostol tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.

Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See "What is the most important information I should know about Mifeprex?"

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See "How should I take Mifeprex?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects.These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596) www.earlyoptionpill.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 3/2016

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

/s/

(b) (6)

03/29/2016

Exhibit B

2011 Mifeprex REMS

Please see REMS updated 3/29/2016

NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg

Danco Laboratories, LLC
PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

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.

II. REMS ELEMENTS

A. Medication Guide

1. A Medication Guide will be dispensed with each MIFEPREX prescription in accordance with 21 CFR 208.24.

2. Please see the appended Medication Guide.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe MIFEPREX will be specially certified.

Danco will ensure that healthcare providers who prescribe MIFEPREX are specially certified.

a. To become specially certified, each prescriber must complete and fax to the MIFEPREX distributor the one-time Prescriber's Agreement, agreeing that they meet the qualifications and will follow the guidelines outlined in the Prescriber's Agreement.

b. The following materials are part of the REMS and are appended:

i. Prescriber's Agreement.

ii. Patient Agreement.

Please see REMS updated 3/29/2016

2. MIFEPREX will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

   Danco will ensure that MIFEPREX will only be available to be dispensed in a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. MIFEPREX will not be distributed to or dispensed through retail pharmacies.

3. MIFEPREX will only be dispensed to patients with documentation of safe use conditions.

   Danco will ensure that MIFEPREX will only be dispensed to patients with documentation of the following safe use conditions:

   a. The patient has completed and signed the Patient Agreement, and the Patient Agreement has been placed in the patient's medical record.

   b. The patient has been provided copies of the signed Patient Agreement and the Medication Guide.

C. Implementation System

The Implementation System will include the following:

1. Distributors who distribute MIFEPREX will be certified. To become certified, distributors must agree to:

   a. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.

   b. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.

2. Danco will assess the performance of the certified distributors with regard to the following:

   a. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.

   b. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

3. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

D. Timetable for Submission of Assessments

Danco will submit REMS assessments to the FDA one year from the date of the approval of the REMS and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the assessment reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco will submit each assessment so that it will be received by the FDA on or before the due date.

MEDICATION GUIDE

Mifeprex® (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is _____.

Be sure to contact your provider promptly if you have any of the following:

Heavy Bleeding. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

Abdominal Pain or "Feeling Sick". If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that

they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this MEDICATION GUIDE.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

* * *

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

M I F E P R E X®
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.

- Ability to diagnose ectopic pregnancies.

- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.

- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.

- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

Please see REMS updated 3/29/2016

ACCOUNT SETUP FORM

MIFEPREX™ (Mifepristone) Tablets, 200 mg; NDC 64875-001-03

To set up your account:

1. Read the Prescriber's Agreement on the back of this Account Setup Form.
2. Complete and sign this form.
3. Fax the completed Account Setup Form to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned in and are usually shipped within 24 hours.
6. Unopened, unused product may be returned for a refund or exchange up to a year after the expiration date.

Billing information

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Shipping information (❑ Check if same as above)

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Additional site locations

I will also be prescribing Mifeprex* at these additional locations:

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

Request additional materials

❑ Medication Guides ❑ Patient Agreements

❑ State Abortion Guidelines ❑ Patient Brochures

Establishing your account (required only with first order)

Each facility purchasing Mifeprex must be included on this form (see additional site locations box above) before the distributor can ship the product. Please read the Prescriber's Agreement on the reverse of this form and sign below.

By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name _____ Signature _____

Medical License # _____ Date _____

Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*Mifeprex is a trademark of Danco Laboratories, LLC.

MIFEPREX™ (Mifepristone) Tablets, 200 mg

Reference ID: 2957855

FDA 0265

OWEB

Mifeprex® (Mifepristone) Tablets, 200 mg

PATIENT AGREEMENT

Mifeprex* (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
    - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
    - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
    - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
    - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
    - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
    - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Please see REMS updated 3/29/2016

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

Please see REMS updated 3/29/2016

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

/s/

(b) (6)

06/08/2011

Exhibit C

2016 Mifeprex REMS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

REMS

Initial REMS approval: 06/2011
Most recent modification: 03/2016

NDA 020687 MIFEPREX® (mifepristone) Tablets, 200 mg

Antiprogestational Synthetic Steroid

Danco Laboratories, LLC
PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

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.

b) Ensuring that Mifeprex is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber.

c) Informing patients about the risk of serious complications associated with Mifeprex

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe Mifeprex must be specially certified.

a. To become specially certified to prescribe Mifeprex, healthcare providers must:

i. Review the Prescribing Information for Mifeprex.

ii. Complete the *Prescriber Agreement Form*. By signing the *Prescriber Agreement Form*, prescribers agree that:

1) They have the following qualifications:

a) Ability to assess the duration of pregnancy accurately

b) Ability to diagnose ectopic pregnancies
c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

2) They will follow the guidelines for use of Mifeprex (see b.i-v below).

b. As a condition of certification, healthcare providers must follow the guidelines for use of Mifeprex described below:

i. Review the *Patient Agreement Form* with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
ii. Sign the *Patient Agreement Form* and obtain the Patient's signature on the *Form*
iii. Provide the patient with a copy of the *Patient Agreement Form* and Medication Guide.
iv. Place the signed *Patient Agreement Form* in the patient's medical record.
v. Record the serial number from each package of Mifeprex in each patient's record.
vi. Report any deaths to Danco Laboratories, identifying the patient by a non-identifiable reference and the serial number from each package of Mifeprex.

c. Danco Laboratories must:

i. Ensure that healthcare providers who prescribe Mifeprex are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements
ii. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

The following materials are part of the REMS and are appended:
- *Prescriber Agreement Form*
- *Patient Agreement Form*

2. Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

a. Danco Laboratories must:

i. Ensure that Mifeprex is available to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber.

ii. Ensure that Mifeprex is not distributed to or dispensed through retail pharmacies or other settings not described above.

3. Mifeprex must be dispensed to patients with evidence or other documentation of safe use conditions.
   a. The patient must sign a *Patient Agreement Form* indicating that she has:
      i. Received, read and been provided a copy of the *Patient Agreement Form*.
      ii. Received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

B. Implementation System

1. Danco Laboratories must ensure that Mifeprex is only distributed to clinics, medical offices and hospitals by or under the supervision of a certified prescriber by:

   a. Ensuring that distributors who distribute Mifeprex comply with the program requirements for distributors. The distributors must:

      i. Put processes and procedures in place to:

         a. Complete the healthcare provider certification process upon receipt of the *Prescriber Agreement Form.*

         b. Notify healthcare providers when they have been certified by the Mifeprex REMS Program.

         c. Ship Mifeprex only to clinics, medical offices, and hospitals identified by certified prescribers in the signed *Prescriber Agreement Form*.

         d. Not ship Mifeprex to prescribers who become de-certified from the Mifeprex Program.

         e. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who (1) attempt to order Mifeprex and are not yet certified, or (2) inquire about how to become certified.

      ii. Put processes and procedures in place to maintain a distribution system that is secure, confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of Mifeprex.

      iii. Train all relevant staff on the Mifeprex REMS Program requirements.

      iv. Comply with audits by Danco Laboratories, FDA or a third party acting on behalf of Danco Laboratories or FDA to ensure that all processes and procedures are in place and are being followed for the Mifeprex REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

   b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of Mifeprex.

2. Danco Laboratories must monitor distribution data to ensure compliance with the REMS Program.

3. Danco Laboratories must audit new distributors within 90 calendar days after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifeprex REMS Program. Danco Laboratories will take steps to address distributor compliance if noncompliance is identified.

4. Danco Laboratories must take reasonable steps to improve implementation of and compliance with the requirements of the Mifeprex REMS Program based on monitoring and assessment of the Mifeprex REMS Program.

5. Danco Laboratories must report to FDA any death associated with Mifeprex whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

Danco Laboratories must submit REMS assessments to FDA one year from the date of the initial approval of the REMS (06/08/2011) and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco Laboratories must submit each assessment so that it will be received by the FDA on or before the due date.

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To set up your account to receive Mifeprex, you must:
1. complete, 2. sign, and 3. fax page 2 of this form to the distributor.

If you will be ordering for more than one facility, you will need to list each facility on your order form before the first order will be shipped to the facility.

Prescriber Agreement: By signing page 2 of this form, you agree that you meet the qualifications below and will follow the guidelines for use. You also understand that if you do not follow the guidelines, the distributor may stop shipping Mifeprex to you.

Mifeprex must be provided by or under the supervision of a healthcare provider who prescribes and meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of Mifeprex. The Prescribing Information is available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Review the Patient Agreement Form with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of Mifeprex in each patient's record.
- Report deaths to Danco Laboratories, identifying the patient by a non-identifiable patient reference and the serial number from each package of Mifeprex.

ACCOUNT SETUP MIFEPREX® (Mifepristone) Tablets, 200 mg; NDC 64875-001-01

TO SET UP YOUR ACCOUNT:

1. Read the Prescriber Agreement on page 1 of this form.
2. Complete and sign this form.
3. Fax this page to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned or faxed and are usually shipped within 24 hours.

Mifeprex® (Mifepristone) Tablets, 200 mg
THE ORIGINAL EARLY OPTION PILL

BILLING INFORMATION

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

SHIPPING INFORMATION ☐ *Check if same as above*

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

ADDITIONAL SITE LOCATIONS *I will also be prescribing Mifeprex* at these additional locations:*

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

REQUEST ADDITIONAL MATERIALS

☐ **Medication Guides** ☐ **State Abortion Guides** ☐ **Patient Brochures** ☐ **Patient Agreement Form**

ESTABLISHING YOUR ACCOUNT *(required only with first order)*

Each facility purchasing Mifeprex must be included on this form (*see additional site locations box above*) before the distributor can ship the product to the facility.

By signing below, you agree that you meet the qualifications and that you will follow the guidelines for use on page 1 of the Prescriber Agreement.

Print Name _____ Signature _____

Medical License # _____ Date _____

FAX THIS COMPLETED FORM TO THE AUTHORIZED DISTRIBUTOR. FAX: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

PATIENT AGREEMENT FORM

Mifeprex® (Mifepristone) Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of Mifeprex*. Both you and the patient must sign this form.*

Patient Agreement:

1. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take Mifeprex on Day 1.
   b. My provider will either give me or prescribe for me the misoprostol tablets which I will take 24 to 48 hours after I take Mifeprex.
3. My healthcare provider has talked with me about the risks including:
   - heavy bleeding
   - infection
   - ectopic pregnancy (a pregnancy outside the womb)
4. I will contact the clinic/office right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - severe stomach area (abdominal) pain
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - stomach pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
5. My healthcare provider has told me that these symptoms could require emergency care. If I cannot reach the clinic or office right away my healthcare provider has told me who to call and what to do.
6. I should follow up with my healthcare provider about 7 to 14 days after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
7. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
8. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
9. I have the MEDICATION GUIDE for Mifeprex. I will take it with me if I visit an emergency room or a healthcare provider who did not give me Mifeprex so that they will understand that I am having a medical abortion with Mifeprex.
10. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name (print):** _____ **Date:** _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for Mifeprex.

Provider's Signature: _____ **Name of Provider (print):** _____ **Date:** _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record.

03/2016

Reference ID: 3909592

DANCO

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

/s/

(b) (6)

03/29/2016

Exhibit D

Nov. 3, 2015, Letter to FDA

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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. Elimination or modification of the REMS

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

FDA 1245

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current REMS is warranted. In our judgement, and based on scientific research and our collective experience, the ETASU are no longer justifiable.

As directed by Congress, the FDA may impose ETASU only when needed for the safe administration of the drug (Section 505-1 of the Federal Food, Drug, and Cosmetic Act). Under the law, the ETASU should be reassessed if they are unduly burdensome to the patient, such as when they impede access to health care by patients, including patients in rural or medically underserved areas (FDCA section 505-1(f)(2)(C)(II)). The ETASU requirements must be commensurate with the specific risks listed in the drug labeling, cannot be unduly burdensome on patient access to the drug, must conform with other components for other drugs with similar serious risks, and must be designed to be compatible with established distribution, procurement, and dispensing systems for drugs (FDCA section 355-1(f)(2)).

Below we review the specific components of the ETASU for mifepristone (Mifeprex) and provide our recommendations for modifying them.

1. Dispensing venues. The ETASU currently require that mifepristone must be dispensed to patients in a clinic, medical office, or hospital. This requirement meets none of the ETASU principles described above.

   - The requirement has no relation to the serious risks described in the "black box warning" on the mifepristone label which are "serious and sometimes fatal infections and bleeding". If these conditions occur, which the label notes happens "very rarely", they begin hours after the drug is ingested and thus cannot possibly be mitigated by requiring that the drug be dispensed in any specific venue. The same is true for all other adverse events listed on the mifepristone label. Notably, the ETASU does not specify that the drug must be ingested in the medical facility, only that it must be dispensed there. In fact, recent research has shown that allowing each patient to ingest the mifepristone in the place and time of her choosing is safe, desirable, and highly acceptable to women who choose the option.[2-4] This research further supports the conclusion that the location where the drug is dispensed has no bearing on risk.
   - The requirement creates a burden to access by necessitating that each providing facility must order supplies of the drug in advance of need, properly store these supplies, and maintain inventory records according to applicable pharmacy laws. These procedures are both financially and logistically onerous, particularly for small facilities. Anecdotal reports suggest that the burden is significant enough to dissuade some providers from offering the service to patients.
   - The requirement is not commensurate with the requirements for distribution of other drugs, including drugs that are much more immediately dangerous than mifepristone. For example, antibiotics, anti-hypertensives, erectile dysfunction drugs, and insulin have been reported to cause serious or fatal reactions shortly after use, yet are all distributed in pharmacies. Furthermore, since each medical abortion patient receives only a sufficient amount of mifepristone for her own abortion, risks such as overdose or redistribution that may be of concern for drugs that are dispensed in pharmacies in multiple doses are not salient for mifepristone. Moreover, mifepristone under the brand name Korlym is mailed by a specialty pharmacy directly to patients with Cushing's syndrome and is taken at home.

   Abortion providers certainly can safely evaluate patients and prescribe mifepristone without having the tablets physically present in their offices. We therefore recommend that this requirement be removed entirely and that mifepristone should be available in retail pharmacies like other prescription drugs.

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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.

Making these changes to the ETASU would render other parts of the REMS obsolete. For example, the distributor certification, as currently written, would become unnecessary if provider certification were not required and pharmacy distribution were permitted. If the ETASU elements are eliminated, the REMS Assessments are no longer needed either. We recommend that the REMS should be discontinued in its entirety, consistent with the FDA's current efforts to decrease disruption to the healthcare system caused when some drugs are subject to distribution requirements that differ from the norm.

The immense volume of data about and experience with mifepristone since its initial approval have demonstrated that this drug is extremely safe and can be appropriately provided by clinicians with routine professional training. Standard professional labeling is clearly sufficient to ensure that its benefits outweigh its risks.

B. Extension of the gestational age limit to 70 days

Substantial evidence demonstrates that the proposed medical abortion regimen is highly effective in the 10th week (64-70 days) of gestation (defined as days since onset of the last menstrual period or estimated days since ovulation + 14). A recent systematic review identified four published prospective studies that recorded data on outcomes of medical abortions performed during this 10th week.[5] We have subsequently found two additional published studies,[6,7] and Gynuity Health Projects recently has conducted two additional studies that are not yet published that also include such data. The published studies were conducted in the United States,[8] Mexico,[9,10] Curaçao,[11] Vietnam,[6,7] and the Republic of Georgia,[7] and the two unpublished studies were conducted in the United States and Mexico. All subjects were treated as outpatients between 2007 and 2015.

The eight studies included a combined total of 634 women treated at 64-70 days of gestation, of whom 587 (91%) provided outcome data (Table 1). Of these women, 92.4% (95% CI 89.9%, 94.4%) had complete medical abortion success (pregnancy termination without resort to surgical intervention), and 3.1% (95% CI 1.9%, 4.9%) had ongoing pregnancies (Table 1). These proportions were not clinically or statistically different from the results obtained in women treated in the 9th gestational week (57-63 days) in the same studies (Table 2). Perhaps more importantly, the complete abortion success rate was comparable to the standard set by the FDA for medical abortion effectiveness in its initial approval of mifepristone in 2000; the proportion of subjects with complete abortion success in the US pivotal trial that supported that approval was 92.1%.[12]

Data from the eight studies also document that medical abortion in the 10th gestational week is safe. Only 7 of the 578 subjects (1.2%, 95%CI 0.5%, 2.5%) treated in that week had serious adverse events, a proportion nearly identical to that among subjects treated in the 9th gestational week (11/1010, 1.1%, 95%CI 0.5%, 1.9%). Two of the studies found that women treated at 64-70 days experienced more side effects, such as vomiting, diarrhea, and weakness, than women treated in the prior week, but these events were managed on an outpatient basis and were self-limited.[8,9] The same two studies also reported data on satisfaction; in these studies, more than 75% of the women treated in the 10th week noted that their medical abortion was satisfactory or would choose it over surgical abortion for a future abortion.

Based on these published and well-known data, medical abortion practice in the United States is rapidly expanding to include provision of the service through 70 days of gestation. The National Abortion Federation updated its Clinical Practice Guidelines in 2013 to recommend the 70-day gestational age limit, and in 2015, 55% of respondents to the annual NAF member survey reported providing medical abortion up to 70 days (Vicki Saporta, President, NAF, personal communication June 10, 2015). Similarly,

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over the past several years, about half of Planned Parenthood affiliates have indicated their intentions to offer services to women up to 70 days, and have provided services to hundreds of women at 64-70 days of gestation (Deborah VanDerhei, National Director, CAPS, Planned Parenthood Federation of America, personal communication June 10, 2015).

Considering the current evidence, we submit that medical abortion is safe and effective through at least 70 days since last menstrual period (LMP) and that a label specifying a maximum gestational age less than that is unnecessarily and arbitrarily conservative. Women who present for abortion in the 10th gestational week currently constitute about 7% of all abortion patients nationally.[13] This is a significant proportion and limitations to access to medical abortion would have significant negative consequences for those women.

Although off-label use of drugs is generally accepted in the United States, many clinicians see FDA labels as guides to appropriate and legally defensible clinical practice. A gestational limit lower than 70 days on the mifepristone label may discourage some clinicians from offering medical abortion to this subgroup of patients. In addition, in states where off-label use of mifepristone is prohibited by law, women at a later gestational age would be entirely prevented from accessing medical abortion. Because of these state laws demanding strict compliance with the label, it is important for the FDA to include on the label all situations where medical abortion is safe and effective. And as a growing number of non-hospital abortion providers offer medical abortion but not surgical abortion,[14,15] these women will need to travel farther and at greater cost to access abortion services at all.

The data presented here are sufficient to establish the efficacy and safety of outpatient medical abortion with mifepristone and misoprostol through 70 days LMP. Including this information on the mifepristone label would be consistent with the FDA's mission to promote public health through the effective and safe use of drugs. Furthermore additional studies of outpatient medical abortion through 70 days LMP are ongoing and we would be happy to forward more information as it becomes available.

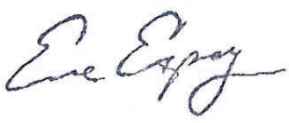
We would be happy to provide further details regarding the data we have presented. We appreciate your consideration of the requests that we have made in this letter.

Respectfully yours,

Kelly Blanchard, MSc
President, Ibis Reproductive Health

Paul Blumenthal, MD, MPH
Professor, Department of Obstetrics and Gynecology
Director, Stanford Gynecology Service
Director, Stanford Division of Family Planning Services and Research
Stanford University School of Medicine

Eve Espey, MD, MPH
Professor and Chair, Department of Obstetrics and Gynecology
Director, Family Planning Fellowship
University of New Mexico School of Medicine



Signatures continue on following page

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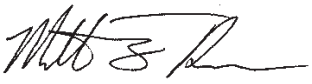
Matthew Reeves, MD, MPH
Medical Director, National Abortion Federation



James Trussell, PhD, B.Phil
Professor of Economics and Public Affairs, Emeritus
Senior Research Demographer, Office of Population Research
Princeton University

Carolyn Westhoff MD, MSc
Sarah Billinghurst Solomon Professor of Reproductive Health
Columbia University Medical Center

Beverly Winikoff, MD, MPH
President, Gynuity Health Projects
Professor, Clinical Population and Family Health
Mailman School of Public Health, Columbia University

Signatures continue on following page

CONFIDENTIAL

Organizational Signatories

American Public Health Association, Population, Reproductive, and Sexual Health Section

National Abortion Federation

Ibis Reproductive Health

Gynuity Health Projects

Exhibit E

Nov. 4, 2015, Letter to FDA

ACOG
THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

Executive Vice President &
Chief Executive Officer
Hal C. Lawrence, III, MD, FACOG
Office: (202) 863-2500
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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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[i] Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70 days gestation. Contraception 2015;92:197-9.
[ii] Cleland K, Smith N. Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data. Contraception 2015;92:179-181.
[iii] Grossman D, Goldstone P. Mifepristone by prescription: a dream in the United States but reality in Australia. Contraception 2015; 92:186–189.
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Exhibit F

Feb. 4, 2016, Letter to FDA

CONFIDENTIAL

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:

FDA 1254

> [E]lements to assure safe use [ETASU] ... shall–
>
> (A) be commensurate with the specific serious risk listed in the labeling of the drug;
>
> ...
>
> (C) considering such risk, not be unduly burdensome on patient access to the drug, considering in particular–
>
> (i) patients with serious or life-threatening diseases or conditions; and
>
> (ii) patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)….[9]

Although the FDA may have decided 15 years ago that the balance of risk and burden came out in favor of restricting mifepristone's indicated use and distribution, today both science and the current conditions surrounding patient access to abortion care call strongly for a reevaluation of the mifepristone label and REMS restrictions, especially its Elements to Assure Safe Use (ETASU).

We support the following changes to the mifepristone label:

- The drug should be indicated for use in medication abortions beyond 49 days gestation.
- The recommended dose regimen should be mifepristone 200 mg followed 24-48 hours later by misoprostol 800 mcg.
- The location where the patient should take these drugs should not be restricted.
- An in-person visit should be indicated as not always necessary for follow-up assessment.
- Any licensed health care provider should be able to prescribe the drug.

We expand below upon further specific changes that should be made based on scientific evidence of mifepristone's safety and efficacy, as well as the numerous burdens on patients' access to abortion care that would be greatly alleviated if the REMS were eliminated and the gestational age indication in the label were increased to 70 days.

1. **Eliminate the REMS and ETASU for mifepristone.**
   a. **Expand dispensing venues.** The ETASU state that mifepristone may only be dispensed to patients in a clinic, medical office, or hospital, and not through pharmacies.[10] The Technical Letter discusses why this requirement is not medically warranted. The requirement should be removed entirely, so that mifepristone can also be distributed via retail pharmacies like other prescription medications, in addition to being directly distributed to providers.

      This requirement significantly curtails mifepristone's potential to expand patient access to abortion care. The up-front costs (including substantial costs for pre-ordering the drug) and logistical requirements (e.g., increased staffing at provider offices) are a burden to providers and, therefore, deter some health care providers from offering medication abortion. When fewer providers are willing to stock mifepristone in their offices because of the REMS and ETASU, fewer patients can access medication abortion. In some cases this requirement may also force the patient to make an unnecessary visit to a clinic, medical office, or hospital to pick up the medication, rather than being able to pick up an order called into a pharmacy. This requirement is especially significant in underserved and rural areas where access to a health care provider is already difficult, and for those with low incomes for whom taking off work or getting to a provider multiple times in short order is impossible due to cost or family needs.[11] The Turnaway Study, a prospective longitudinal study conducted by Advancing New Standards in Reproductive Health (ANSIRH) at the University of California-San Francisco examining the effects of unintended pregnancy on individuals' lives, demonstrates that the majority of people who seek abortion care are already in difficult financial situations, and are

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.

These burdens are often increased for patients living in rural and other medically underserved areas. In 2008, 33% of all abortion patients traveled more than 25 miles to obtain care, and 74% of all patients living in rural areas traveled at least 50 miles to obtain the procedure.[23] Medical technology and telemedicine have advanced considerably since 2000,[24] and a growing body of evidence shows that alternatives to in-person follow-up, such as serum chorionic gonadotropin (hCG), multi-level pregnancy tests, and telephone counseling are safe, effective, and improve access and satisfaction for patients.[25,26,27]

2. **Increase the gestational age for indicated use on the label.**
The current label indicates use of mifepristone through 49 days after the start of the patient's last menstrual period (LMP). The Technical Letter discusses the substantial evidence demonstrating that the evidence-based medication abortion regimen is highly effective later than 49 days LMP, through at least the 10th week (64-70 days) of gestation.[28,29,30] The National Abortion Federation's (NAF) annual *Clinical Policy Guidelines*, which NAF develops by consensus based on a rigorous review of current medical literature and known patient outcomes, recommend that an evidence-based medication abortion regimen be used through 70 days LMP.[31] The time between 49 and 70 days LMP is critical for patient access, as approximately 30% of women who seek an abortion present for care during this time, according to the Centers for Disease Control.[32]

Consider the current legal and social climate

The overall legal and social climate around abortion care intensifies all of the burdens that the mifepristone REMS places on patients and makes it even more critical that the FDA lift medically unnecessary restrictions on the drug. Since mifepristone's approval, a multitude of laws and regulations at the federal and state level have dramatically restricted access to abortion care. In the first five years of this decade alone, states enacted 288 abortion restrictions – more than the entire previous decade.[33] These restrictions are typically unsupported by medical evidence and serve only to reduce access to abortion care.[34] In 2000, the Guttmacher Institute, a nonpartisan research and policy organization that seeks to advance sexual and reproductive health and rights and ensure the highest standard of sexual and reproductive health care, considered 13 states to be hostile to abortion, meaning that those states had 4-5 types of restrictions on abortion. In 2014, the number of states considered hostile had more than doubled, now including more than half of all states.[34]

Providers have increasingly been forced to close their doors as a result of mounting restrictions. There were about 1,800 abortion providers in the U.S. in 2000. Stand-alone abortion clinics constituted 447 (25%) of all providers in 2000, and those clinics provided 71% of all abortions.[35] By 2008, only 378 abortion clinics were still providing 70% of abortions.[36] Abortion clinic closures have accelerated since 2008, as lawmakers began passing restrictions at an unprecedented rate.[37] The Associated Press estimated in June 2015 that 70 abortion clinics had closed in a dozen states since 2010.[38] This wave of state restrictions and clinic closures has continued unabated in the last five years.

Some of these measures specifically block access to medication abortion by invoking the FDA-approved label. North Dakota, Ohio, and Texas currently require mifepristone to be administered solely according to the regimen that appears on the FDA label.[39] The Arkansas legislature just passed a similar law in 2015, though a federal judge issued a temporary restraining order blocking enforcement of the law until a hearing on March 14, 2016.[40] In these states, mifepristone cannot be prescribed in accordance with evidence-based practices developed in the last 15 years,* which improve patient access in multiple ways:

- enabling patients to take a lower dose of mifepristone, resulting in fewer side effects and lower cost;

*The one deviation that Texas allows from the label is one other dosage amount of Mifeprex and misoprostol.[39]

- allowing patients to take mifepristone, misoprostol, or both at home, and/or confirm termination of pregnancy at home, resulting in fewer visits to the provider;
- and offering medication abortion to patients later than 49 days LMP.[3]

Studies have also shown that these "label laws" have had a negative impact on patient access to abortion. For example, a recent study showed that after passage of laws that restricted use of mifepristone to the FDA label in Texas and Ohio, medication abortion declined dramatically while it rose in New York and California, states without restrictive laws.[41] Furthermore, these laws run counter to the FDA's own guidance, which states that a "package insert is informational only."[42,43,44] As long as the FDA-approved label diverges from evidence-based regimens, states can hide behind it as they restrict access to abortion. If the FDA does not update mifepristone's label to reflect the most current, evidence-based practice, the number of women adversely affected will only increase as additional states pass laws to exploit this discrepancy.

Other state restrictions are not specific to medication abortion, but affect all kinds of abortion care, including access to mifepristone. These medically unnecessary restrictions include the following: requirements that facilities where abortion is provided meet standards for ambulatory surgical centers; physician admitting privileges at local hospitals; and requirements that the patient and prescribing clinician must be in the same physical location, prohibiting the use of telemedicine technology. On top of these legal restrictions, anti-abortion stigma, harassment, and violence deter many health care professionals from providing abortion care. Authorizing distribution of mifepristone in pharmacies could diminish the impact of these barriers and allow providers to offer abortion care without fear of retaliation.

These restrictions, and the concomitant politicization and stigmatization of abortion care, have also seeped into other aspects of health care and prevented progress on the use of mifepristone for other indications. Removing the REMS program would make mifepristone more readily available for non-abortion therapies as well.[45,46]

In summary, the burdens on patient access to medication abortion, exacerbated by the REMS requirements placed on mifepristone, strongly outweigh any medical risk to the patient associated with the drug. In this climate of legal restrictions, clinic closures, and mounting stigma, it is increasingly important that any regulation of mifepristone be based solely on medical evidence, rather than the discretion of politicians who are determined to restrict access to abortion at any price. We recognize that the FDA is not responsible for most restrictions on abortion access. However, whenever the FDA evaluates indications and restrictions on an approved product, it does so in the context of the real-world circumstances in which the product is sold and the condition is treated. We believe this is vital in the case of mifepristone in particular, where the broad landscape of laws regulating abortion has measurable negative impact on the clinical provision of abortion care.

Mifepristone continues to hold immense promise for patient access to a safe and effective early abortion option, but medically unnecessary regulations are impeding its full potential. Extensive scientific and clinical evidence of mifepristone's safety and efficacy, and the ever-increasing burden on patient access to abortion care, clearly demonstrate that mifepristone's REMS program is not needed to protect patients. In light of the FDA's statutory mandate from Congress to consider the burden caused to patients by REMS, and the agency's own stated commitment to ensuring that drug restrictions do not unduly burden patient access, we ask that the FDA lift mifepristone's REMS and amend the label to extend the indicated use to 70 days.

Sincerely,

Advancing New Standards in Reproductive Health (ANSIRH), Department of Obstetrics, Gynecology & Reproductive Sciences, University of California, San Francisco
American Civil Liberties Union
Association of Reproductive Health Professionals
Bixby Center for Global Reproductive Health, Department of Obstetrics, Gynecology & Reproductive Sciences, University of California, San Francisco
Cambridge Reproductive Health Consultants
Carafem
Center for Reproductive Rights
Center on Reproductive Rights and Justice at the University of California, Berkeley, School of Law
Feminist Majority Foundation
Guttmacher Institute
Gynuity Health Projects
Ibis Reproductive Health
Jacobs Institute of Women's Health
Legal Voice
Medical Students for Choice
NARAL Pro-Choice America
National Abortion Federation
National Advocates for Pregnant Women
National Institute for Reproductive Health
National Latina Institute for Reproductive Health
National Network of Abortion Funds
National Partnership for Women and Families
National Women's Health Network
National Women's Law Center
Planned Parenthood Federation of America
Physicians for Reproductive Health
Provide
Reproaction
Reproductive Health Technologies Project
Society of Family Planning

cc:
Valerie Jarrett, Chair, White House Council on Women and Girls
Tina Tchen, Executive Director, White House Council on Women and Girls
Jordan Brooks, Deputy Executive Director, White House Council on Women and Girls
Nancy C. Lee, M.D., Deputy Assistant Secretary of Health, Women's Health, Director of the Office on Women's Health, Department of Health and Human Services
Bobby Clark, Counselor for Public Health and Science, U.S. Department of Health and Human Services, Office of the Secretary

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[43] Agency Request for Comments: Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 Fed. Reg. 59820-01 (Nov. 18, 1994) ("FDA has long recognized that physicians and other health care professionals may prescribe approved therapies for unapproved uses").
[44] Agency Comments on Proposed Rule: Applicability of IND Requirements, 52 Fed. Reg. 8798, 8803 (final rule Mar. 19, 1987) (codified at 21 CFR § 312.2) ("As noted in the preamble to the proposed rule, it was clearly the intent of Congress in passing the Federal Food, Drug, and Cosmetic Act that FDA not regulate the practice of medicine, which the agency has consistently viewed as including the use by physicians of marketed drugs for unlabeled indications in the 'day-to-day' treatment of patients. Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling. Control of the practice of medicine in these cases is primarily exercised through State laws affecting medical licensing and practice and through products liability law").
[45] Dzuba IG, Grossman D, Schreiber CA. Off-label indications for mifepristone in gynecology and obstetrics. *Contraception,* 2015;92:203-05, doi: 10.1016/j.contraception.2015.06.021 (showing that data from around the world suggests mifepristone could be used to treat patients with a wide variety of cancers, tumors, and other hormone-sensitive conditions who have exhausted other standard treatments).
[46] Mifepristone Compassionate Use Program. Feminist Majority Foundation website (discussing a program that has been able to help treat a small cadre of eligible patients, but must contend with FDA-mandated paperwork that is onerous to most physicians and creates needless delays in quickly and effectively accessing a potentially life-saving treatment option). http://www feminist.org/rrights/compassionateuse.asp. Accessed December 21, 2015.

Exhibit G

Feb. 25, 2016, Letter from FDA to Plaintiff Society of Family Planning et al.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Services

Food and Drug Administration
Silver Spring, MD 20993

February 25, 2016

Jessica Arons, J.D.
President and Chief Executive Officer
Reproductive Health Technologies Project
1634 Eye Street, NW, Suite 650
Washington, DC 20006
jarons@rhtp.org

Dear Ms. Arons,

Thank you for your letter dated February 4, 2016, to Dr. Ostroff, Dr. Califf, and me with recommendations to lift the Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex (mifepristone), and to extend the indicated use of Mifeprex through a gestational age of 70 days. Dr. Ostroff has asked me to respond on behalf of the FDA because the Center for Drug Evaluation and Research is responsible for regulating all drugs, including mifepristone. Please share this response with your cosigners.

In your letter, you strongly encouraged FDA to revise the mifepristone label and eliminate the REMS restrictions, especially the Elements to Assure Safe Use, which includes the prescriber and patient agreements. You requested that the dose regimen be changed to mifepristone 200 mg followed 24-48 hours later by misoprostol 800 mcg. You also recommended not restricting the location where the patient should take these drugs and stated that an in-person visit is not always necessary for a follow-up assessment. Moreover, you proposed that any licensed health care provider should be able to prescribe mifepristone, and that it be available through pharmacies as well as provider offices.

Your letter has been shared with the appropriate FDA staff and will be carefully reviewed.

Thank you again for contacting us.

Sincerely,

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration

Exhibit H

2013 Mifeprex REMS Review

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

(b) (6)

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	October 10, 2013
Drug Name(s):	Mifeprex (mifepristone) 200 mg tablets
Therapeutic Class:	progesterone-receptor modulator
Dosage and Route:	Mifepristone 600 mg as a single oral dose followed by misoprostol 400 micrograms on Day 3
Application Type/Number:	NDA 020687/Danco Laboratories
(b) (6) #:	(b) (4) 2012-1287

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

EXECUTIVE SUMMARY

This review evaluates if the risk evaluation and mitigation strategy (REMS) for Mifeprex (mifepristone 200 mg tablets) continues to be necessary to ensure the benefits of the product outweigh its risks.

Mifeprex was approved on September 28, 2000 with a restricted distribution program requiring prescribers attest that they are knowledgeable about the safe and appropriate use of Mifeprex. The program was approved as a REMS on June 8, 2011. The goals of the REMS are:

- 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.

Since the approval of Mifeprex, safety concerns have been reported by certified prescribers, including serious infection and hemorrhage sometimes leading to the need for transfusions, hospitalization, and death. We reviewed the current Mifeprex safety data and researched what factors may affect its safe use for patients. Our key findings include that:

- The overall safety profile of Mifeprex has not changed over the last 6-7 years and is consistent with current product labeling.
- There have been a small number of serious complications associated with Mifeprex reported and this is likely reflective of the use of Mifeprex within a system of knowledgeable healthcare providers, safe use protocols, and proper patient counseling.
    - Planned Parenthood and other family planning clinics account for the majority of Mifeprex use. Planned Parenthood implements the REMS requirements (b) (4).

Accurate gestation dating, patient education, dispensing Mifeprex directly to the patient during the office visit, and timely access to medical care remain important components to ensure the safe use of Mifeprex in order to maintain the current safety profile. Medical abortion accounts for the minority of abortions in the U.S. Similarly, training opportunities in medical abortion appear limited and are less available than surgical abortion experience. Given this relative lack of familiarity and experience with medical abortion, a restricted distribution program that reinforces the necessary skills and appropriate care (i.e., counseling and follow-up) is necessary to assuring safe use of Mifeprex. It is not likely that the essential safe use conditions will be maintained to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events. For these reasons, we believe the Mifeprex REMS provides the foundation to ensure the implementation of these safe use conditions with Mifeprex use.

(b) (6) therefore recommends that the existing elements of the REMS be maintained. Specifically, prescriber certification and dispensing limited to certain healthcare settings provide a framework to ensure that the benefits of Mifeprex outweigh its risks in an appropriate patient population.

INTRODUCTION

This review evaluates if the risk evaluation and mitigation strategy (REMS) continues to be necessary to ensure the benefits outweigh the risks for Mifeprex (mifepristone 200 mg tablets).

(b) (4)

During a (b) (6) meeting on October 4, 2012[2], the Center Director requested that the REMS for Mifeprex be re-evaluated to determine if a REMS continues to be necessary to ensure that the benefits outweigh the risks, (b) (4)

The merits of (b) (4) for mifepristone 200 mg is addressed in a separate memorandum.

1 BACKGROUND & REGULATORY HISTORY OF MIFEPREX REMS

On September 28, 2000, Mifeprex was approved for the medical termination of intrauterine pregnancy through 49 days' gestation under 21 CFR 314.520 Subpart H.[3] According to the September 28, 2000 (b) (6) review, "the success of medical termination of pregnancy decreased with advancing gestational age and incidence of adverse events increased with advancing gestational age." In addition, the review states that timely access to medical care to manage serious complications is necessary. The (b) (6), 's approval memo states, "[t]he 1996 advisory committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregnancies (and other requirements), goals of safe and appropriate use may be achieved."[4]

As a result, FDA concluded Mifeprex must be available only through a restricted distribution program and required the program under Subpart H.

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1 (b) (4) (b) (4)

2 (b) (4), (b) (6)

3 Mifeprex Approval Letter signed September 28, 2000.

4 (b) (6) (b) (6) Memo. Signed September 28, 2000.

In 2007, Congress amended the FD&C Act to give FDA the authority to require a REMS when necessary to ensure that the benefits of a drug outweigh its risks.[5] Mifeprex was included on the list of products deemed to have in effect an approved REMS.[6]

The Mifeprex restricted distribution program was approved as a REMS on June 8, 2011 and contains the following elements:[7, 8]

A. 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.

B. Medication Guide

C. Elements to Assure Safe Use, including:

a. Healthcare providers who prescribe Mifeprex will be specially certified by agreeing or attesting to the conditions set forth in the Prescriber Agreement.

b. Mifeprex will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

c. Mifeprex will only be dispensed to patients with documentation of safe use conditions.

D. An Implementation System that requires Danco to:

a. Certify distributors. To become certified, distributors must agree to:

i. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.

ii. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.

b. Assess the performance of the certified distributors with regard to the following:

i. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.

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[5] Food and Drug Administration Amendments Act (FDAAA) of 2007, Pub. L. No. 110-85, Title IX, Subtitle A, Section 901, 121 Stat. 823 (2007).

[6] See Identification of Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (REMS) for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16313 (Mar. 27, 2008).

[7] Memorandum of meeting minutes for April 28, 2011 meeting between Danco and FDA. Signed by (b) (6) on June 3, 2011.

[8] Mifeprex REMS Approval Letter. Signed by (b) (6) on June 8, 2011.

ii. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

c. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

E. A Timetable for Submission of Assessments that requires Danco to submit REMS assessments to FDA one year from the date of approval of the REMS and every three years after.

The next REMS assessment is due June 2015.

2 SAFETY PROFILE OF MIFEPREX

2.1 BACKGROUND

Abortion is one of the most common procedures undergone by women of reproductive age in the United States.[9] Since 1969, the Centers for Disease Control and Prevention (CDC) has conducted abortion surveillance to document the number and characteristics of women obtaining legal, induced abortions. The 2009 data is the most recent year available. The CDC requests data from 52 reporting areas (i.e., 50 states, District of Columbia, and New York City). The areas provide information voluntarily; 45 areas reported data every year from 2000 – 2009. In most states, collection of abortion data is facilitated by the legal requirements for hospitals, facilities, and physicians to report abortions to a central health agency. These health agencies in turn voluntarily provide aggregate data to the CDC. For medical abortions, the CDC abortion surveillance summary does not include specific information on what medications and dosages are used.

A total of 784,507 abortions were reported to the CDC for 2009. Approximately 17% (16.2% ≤ 8 weeks' gestation, 0.9% >8 weeks' gestation) of abortions were reported as medical.[10,11] This is a slight increase from 2008 data (14.1% ≤ 8 weeks' gestation, 0.7% >8 weeks' gestation).[12]

In 2009, most (64.0%) abortions were performed at ≤8 weeks' gestation, and 91.7% were performed at ≤13 weeks' gestation. Among areas that reported data every year during 2000 – 2009, the percentage of abortions performed at ≤ 8 weeks' gestation increased 12% from 2008 to 2009.

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[9] Jones K et al. Abortion in the United States: Incidence and access to services, 2005. Perspect Sex Reprod Health 2008;41(1): 6-16.

[10] "the administration of medication or medications to include an abortion; at ≤8 weeks' gestation, typically involves the use of mifepristone and misoprostol; at >8 weeks' gestation, typically involves the use of vaginal prostaglandins". CDC does not report on specific medications and dosages used.

[11] Pazol K et al. Abortion Surveillance – United States, 2009. MMWR Surveillance Summaries 2012;61:1-44. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6108a1_htm?s_cid=ss6108a1_w#Tab24.

[12] Pazol K et al. Abortion Surveillance – United States, 2008. MMWR Surveillance Summaries 2011;60:1-40. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6015a1_htm?s_cid=ss6015a1_w.

2.2 SERIOUS COMPLICATIONS ASSESSED THROUGH THE REMS

Serious complications[13] assessed through the Mifeprex REMS include:

1. Hospitalizations
2. Transfusions of 2 or more units of packed cells or whole blood or having a hemoglobin of 6 gm/dL or less or a hematocrit of 18% or less
3. Serious infection, sepsis
4. Death
5. Other serious and unexpected adverse events

As of October 31, 2012, approximately 1.88 million women in the U.S. have been treated with Mifeprex for termination of pregnancy with 2,740 adverse events reported cumulatively (14 deaths, 768 hospitalizations, 66 ectopic pregnancies, 416 reports of blood loss requiring transfusion, and 308 infections [57 severe]). The overall estimate of a hospitalization over time is 1 in 2,448 patients. The following tables provide an analysis of the reporting rates of these adverse events over time.

Table 1 provides US Mifeprex use and adverse reporting rates per 100,000 uses in 2-year time intervals over the past 6 years (October 2006 through October 2012).

[13] Although ongoing pregnancies (confirmed and unconfirmed) are assessed in REMS assessment reports, ongoing pregnancy is not considered a serious complication because it usually reflects an incomplete abortion which is sometimes part of the medical abortion process.

Table 1: US Reporting Rates for Serious Adverse Events with Mifeprex per 100,000 uses from October 2006 through October 2012

Time Period	Use	Adverse events	Deaths	Hospital-izations	Trans-fusions	Ectopic Pregnancies	Infection	Severe[14] Infection
10/06 to 10/08	(b) (4) K*	357	1	105	63	9	48	8
Rate per 100 K	NA	(b) (4)						
10/08 to 10/10	(b) (4) K	600	4	187	103	18	71	10
Rate per 100 K	NA	(b) (4)						
10/10 to 10/12	(b) (4) K	704	0	213	115	11	67	17
Rate per 100 K	NA	(b) (4)						

NA= not applicable
*K = 1,000; for example, (b) (4) K = (b) (4). All rates are per 100,000 uses of the drug.
Source: the data here is extracted directly from the quarterly FDA reports using the same categories.

Table 2 provides an adverse event analysis for the most recent 18 months of available data from April 30, 2011 through October 31, 2012.

[14] This category includes endometritis (involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as Chlamydia infections and gonorrhea, cystitis and women with toxic shock syndrome not associated with a pelvic infection.

Table 2: Adverse Event Analysis - per (b) (6) US Postmarketing Adverse Event Summary from April 30, 2011 through October 31, 2012.

Time Period	~ # Women*	AEs reported	Deaths	Hospitalizations	Trans-fusions	Infections (severe)	Hospitalization Rate per women
4/30/11-10/31/11	(b) (4)	178	0	66	27	13 (5)	1 hospitalized per (b) (4) women
10/31/11 - 4/30/12		185	0	52	26	14 (3)	1 hospitalized per (b) (4) women
4/30/12-10/31/12		170	0	38	24	15 (1)	1 hospitalized per (b) (4) women

*Estimate based on above table showing (b) (4) U.S. women per month being treated with Mifeprex for termination of pregnancy from Feb 2011 through Oct 2012.

DEATHS

An overview of each of the US reports with a fatal outcome following mifepristone use for termination of pregnancy from approval in 2000 through January 9, 2013 is provided in Appendix A. Fourteen deaths in US women have been reported since approval. The last reported death occurred in March 2010. In half of the reported deaths, the cause of death was related to infection/sepsis. Two deaths were related to a ruptured ectopic pregnancy. Mifeprex is neither indicated for nor effective for terminating ectopic pregnancy.[15]

3 MIFEPRISTONE USE

3.1 MIFEPREX (MIFEPRISTONE 200MG TABLETS) UTILIZATION

Drug use information is not available to FDA through commercial databases for drugs distributed through closed distribution systems. Sales distribution data for Mifeprex is only available from the sponsor (Danco). Danco provides an estimate of the number of women who have used mifepristone in the US for termination of pregnancy on a periodic basis and as part of the REMS assessment. The (b) (6) has summarized the use data along with adverse event reporting information on a quarterly to semi-annual basis. A version of this document is available on FDA.gov (last report posted - April 2011).[16] The table below is based on the use data provided by Danco and documented in the (b) (6) summaries.

[15] "Mifeprex is contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifeprex is not effective for terminating these pregnancies." Mifeprex [package insert] New York, NY. Danco Laboratories, LLC;2005.

[16] Available at http://www fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323 htm 222. Accessed January 27, 2013.

Table 3: Estimate of the number of women who have used mifepristone in the US for termination of pregnancy per month				
End of Month/Year	Cumulative number of women from approval	Change	Number of Months	N/month
Mar 2006	575,000			
June 2006	612,000	37,000	3	12,300
May 2007	750,000	138,000	11	12,500
Jan 2008	855,000	105,000	8	13,100
Sept 2008	979,000	124,000	8	15,500
May 2009	1,100,000	121,000	8	15,100
Dec 2009	1,230,000	130,000	7	18,600
July 2010	1,350,000	120,000	7	17,100
Jan 2011	1,460,000	110,000	6	18,300
April 2011	1,520,000	60,000	3	20,000
Aug 2011	1,600,000	80,000	4	20,000
Dec 2011	1,680,000	80,000	4	20,000
Oct 2012	1,880,000	200,000	10	20,000

Danco states that the majority of drug/use ((b) (4)%) is distributed to/by Planned Parenthood and other family planning clinics. The remainder is distributed through hospitals and private practices. An independent study published in 2009 found 88% of Mifeprex for abortions was dispensed through clinics.[17]

3.1.1 Korlym (mifepristone 300mg tablets)

Korlym was approved without a REMS by FDA on February 17, 2012 for the treatment of Cushing's syndrome. However, the sponsor distributes Korlym through a single specialty pharmacy and agreed to provide use data as part of a PMR "to better characterize the incidence rates of adverse events with Korlym." Preliminary data from the first 6 months of marketing of Korlym indicated that (b) (4) patients under the care of (b) (4) prescribers received Korlym. Most of the use ((b) (4) of (b) (4) patients) was for the treatment of Cushing's syndrome. (b) (4)

[17] Finer L, Wei J. Mifepristone and abortion access in the U.S. Obstet Gynecol 2009;114:623-40.

[redacted] Additional information on the [redacted] code is pending.

3.2 FACTORS AFFECTING SAFE USE OF MIFEPREX

3.2.1 REMS

As described in Section 1.1, in order to obtain Mifeprex, healthcare providers must be willing to enroll in the REMS program by attesting to have the necessary skills and agreeing to comply with the program requirements. Based on the May 30, 2012 REMS Assessment submission, the following prescriber data were provided by Danco:

- Cumulative number of prescribers enrolled
- Number of new prescribers enrolled during reporting period
- Number of prescribers ordering Mifeprex during reporting period

[redacted]

According to a study published in 2009 by Finer and Wei, between November 2000 and May 2007, among physicians who had ever provided mifepristone, 67% were obstetrician-gynecologists and 13% were family practice physicians.[17] Danco does not collect practice specialty information.

3.2.2 Planned Parenthood

Planned Parenthood and other family planning clinics account for the majority (e.g., [redacted]) of Mifeprex use. Planned Parenthood has implemented [redacted]

[redacted]

[redacted]

[18] Fjerstad M, et al. Rates of Serious Infection after Changes in Regimens for Medical Abortion. NEJM. 2009;361-145-51.

Fjerstad et al performed a retrospective analysis assessing the rates of serious infection in the US after medical abortion. The rate of serious infection after medical abortion declined by 93% after these changes were implemented (from 0.93 per 1000 to 0.06 per 1000).[18]

In 2007, FDA stated that there was not "sufficient information to recommend the use of prophylactic antibiotics for women having a medical abortion." The current American College of Obstetricians and Gynecologists Practice Bulletin on medical abortion states that "no data exist to support the routine use of preventative antibiotics for medical abortion." The Practice Bulletin recommends oral or vaginal administration of misoprostol.[19]

The current Mifeprex professional labeling does not include information on antibiotic prophylaxis and does recommend oral (as opposed to vaginal) administration of misoprostol (in a dose different from current standard practice outlined in the ACOG Practice Bulletin and Planned Parenthood protocol).

3.2.3 Physician Training in Induced Abortion[20,21,22]

In 1996, in response to data indicating that the (1) age of practicing obstetricians who provided the majority of pregnancy terminations was rising (older than 65 years) and (2) the majority of counties in the U.S. lack of abortion providers, the Accreditation Council for Graduate Medical Education (ACGME) required obstetrics and gynecology residency programs to provide training *opportunities* in induced abortion.

In 1998 and 2004, a survey was mailed to all obstetrics and gynecology residency program directors in an effort to characterize the availability of abortion training. In 1998, 46% of respondents reported routine[23] training. In 2004, 51% of directors reported routine training, 39% reported optional training, and 10% reported no training. Of those programs with routine training, 50% reported training in termination practices -- the most common were first-trimester surgical abortion (85%), followed by medical abortion (59%), second trimester induction (51%), and dilation and extraction (36%).[20]

A survey[22] conducted in 2007 of final year obstetrics and gynecology residents sought to determine which abortion procedures residency graduates had received training. Respondents reported higher routine, on-site participation in training on surgical abortion procedures (range 65.6% - 85.2%) compared to mifepristone (52.3%). Routine participation in off-site mifepristone training was higher (72.7%). Ten percent of respondents reported that no training was available on mifepristone use, which is consistent with the 2004 study of residency program directors.

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[19] ACOG Practice Bulletin: *Compared with the FDA-approved regimen, mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 µg of misoprostol vaginally are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP.*

[20] Eastwood KL, et al. Abortion training in United States obstetrics and gynecology residency programs. Obstet Gynecol 2006;108;303-8.

[21] Greenberg M. et al. Barriers and enablers to becoming abortion providers: the reproductive health program. Fam Med 2011;44(7):493-500.

[22] Jackson CB, Foster AM. Ob/Gyn training in abortion care: results from a national survey. Contraception 2012;86:407-417.

[23] Routine training was defined as "required training unless residents express moral objections."

The ACGME requirements for family medicine residents do not include training in medical abortion but residents must be "trained to competency" in "options counseling for unintended pregnancy." A similar survey to characterize the availability of abortion training in family medicine residencies reported 49% provide some type of abortion training.

From 1999 through 2005, the Department of Family Medicine at the University of Rochester Medical Center operated the Reproductive Health Program (RHP), a national elective abortion training program aimed to address a gap in training to all US medical students, residents, advanced practice clinicians, and physicians in practice. A study published in 2012 interviewed RHP trained providers in 2008-2009. A total of 58.8% of respondents reported providing abortions since training, with most occurring in high-volume abortion clinic settings. Of those who had provided abortions, most had performed more than 50 surgical or medical abortions. More than 90% of abortion providers reported having liability insurance that covers abortion, colleague support, ease of obtaining medications and/or equipment, reimbursement, and administrative and/or staff support at the site where they provide abortions. Relative to providers, the greatest barriers to providing an abortion reported by non-providers were lack of skills, concerns about liability, and difficulty obtaining supplies.[21] Although these data were limited to RHP trainees, data are consistent with data from other sources and provides additional insight into what facilitates abortion care and barriers.

4 CONSIDERATIONS REGARDING THE NEED FOR A REMS

4.1 SAFETY CONSIDERATIONS

In general, the intended patient population for Mifeprex is healthy. Medical abortion, similar to surgical abortion, is associated with potentially serious adverse events. Since the approval of Mifeprex, safety concerns have been identified through enhanced surveillance and reporting by certified prescribers. Use of Mifeprex is associated rarely with serious infection and hemorrhage sometimes resulting in transfusions, hospitalization, and death. Serious infections and deaths resulted in labeling changes in 2004 and 2005. There have been no new safety concerns identified with Mifeprex since that time and the serious complications being reported now are consistent with labeling. Moreover, these complications with Mifeprex are consistent with what one can expect with spontaneous abortion and surgical abortions.[24,25] The serious complications that arise can be managed if recognized in a timely manner.

(b) (6) believes that the current safety profile is reflective of an effective system in place with knowledgeable prescribers primarily using Mifeprex within that system guided by standard protocols. It is not likely that the current safe use conditions will persist to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events if the REMS was eliminated. Because Mifeprex prescribing occurs in a limited number of healthcare settings and training is not uniformly provided in physician residencies, there is no data

[24] Mifeprex [package insert] New York, NY. Danco Laboratories, LLC;2005.

[25] Grimes, DA and Raymond, EG. Medical Abortion in Adolescents, *BJM* 2011;342:d2185.

indicating that the appropriate use of Mifeprex has become an ingrained part of "standard medical practice". The "standard" is for Mifeprex to be prescribed within these family planning clinics or by qualified physicians in a private setting. However, if the REMS is eliminated, use would no longer be restricted to these practice settings with knowledgeable prescribers, and use outside the current effective "standard practice " setting could occur.

If the REMS for Mifeprex is eliminated, there would be no restrictions for dispensing and Mifeprex (or any generics that may be approved in the future) could be made available (depending on the manufacturer's business decisions) in the same manner as any prescription drug product. Such a change could result in 1) treatment delays which are problematic given the importance of gestational timing on the safe and effective use or 2) inappropriate prescribing (e.g., ectopic pregnancy) by less experienced practitioners.

4.2 MONITORING CONSIDERATIONS

It is not known how adverse event reporting will change if a REMS is eliminated. Planned Parenthood and the manufacturers would not be required to continue the same level of reporting of serious complications. Data on deaths from infection after Mifeprex use would be available through the CDC. The CDC conducts regular surveillance for maternal mortality and morbidity associated with pregnancy and abortion, including deaths from infection following a medical abortion or any pregnancy event. We note the abortion surveillance summaries published by CDC can have a lag time of up to four years.

Reporting may not be important if it was determined that the risks no longer warrant additional safe use requirements. However, given the public interest this medication generates, it is likely information inquiries will continue. If the REMS is eliminated, FDA will be less informed of adverse events that occur with Mifeprex or its generics.

4.3 DISTRIBUTION CONSIDERATIONS

The [redacted] (b) (6)) believes that Danco would continue some sort of restricted distribution even if FDA no longer requires it. It is not known how new generic sponsors/manufacturers would choose to distribute mifepristone if no restrictions were required by FDA. Even if not required and both innovator and generic manufacturers choose to continue to dispense mifepristone through clinics and medical offices, this would be based on the various manufacturers business decisions and subject to change at their discretion.

Without a REMS, prescriber and patient usage information may be more complex to obtain and less precise than the current data. Furthermore, if the sponsor(s) chose to maintain a closed distribution system, it would be difficult for FDA to track use data in the absence of being provided data directly from the sponsor(s).

4.4 CONFIDENTIALITY/PRIVACY

Confidentiality and patient privacy are significant issues with Mifeprex, but not generally a factor when determining the need for a REMS. The availability of Mifeprex through retail pharmacies could reduce patient/prescriber confidentiality by adding the need to write and fill a prescription. Concerns regarding protests or targeting may deter retail pharmacies from stocking Mifeprex.

The purpose of a REMS is to ensure the benefits of the drug outweigh its risks. While we remain concerned about confidentiality and concerned regarding the personal safety of the prescribers, pharmacists, and patients, it does not meet the criteria for requiring a REMS. Moreover, manufacturers could decide to protect prescriber and patient confidentiality without a REMS.

5 IMPACT OF REMS ELEMENTS AND THEIR REMOVAL

The risk mitigation tools that are part of the Mifeprex REMS are physician certification and controlled access (or restricted distribution). A Mifeprex prescriber must agree that he/she meets the required qualifications to assure the drug is used safely and appropriately. A prescriber self-certifies by completing a one-time enrollment form. This enrollment or certification requirement is the tool that provides controlled access to Mifeprex. Without restricted distribution, a prescriber using Mifeprex would not have to attest to having certain skills, agree to provide counseling on how to handle adverse events, provide Mifeprex during the office visit, document certain information/activities, or report serious complications.

5.1 PRESCRIBER CERTIFICATION

This Prescriber Agreement is a one-time event with limited burden. Prescriber certification probably has the most influence of the three ETASUs in addressing safe use and limiting access to Mifeprex because this element requires physicians to attest to having certain skills, agree to abide by the program requirements including reporting of serious adverse events, and complete an additional step (e.g., the enrollment form) in the usual drug procurement process.

Eliminating this element opens access to any prescriber. Therefore, it is possible that physicians and advanced practice healthcare providers (e.g., physician assistants, nurse practitioners) who are not familiar with Mifeprex and/or practice outside of facilities with established protocols may prescribe Mifeprex; a factor that could contribute to an increase in serious complications.

5.2 RESTRICTED TO CERTAIN HEALTHCARE SETTINGS

This element limits distribution by preventing the distribution of Mifeprex through retail (including mail order and internet) pharmacies. If this restriction was removed, any pharmacy could stock the drug and prescribers would no longer have to stock Mifeprex. In a "worst case" scenario, the following *could* occur:

- patients are not properly counseled about the serious complications and what to do in the event that they experience an adverse event,
- patients may not pick-up the prescription – failing to initiate the abortion in a timely manner resulting in ineffective or inappropriate use of the drug or potentially an increased incidence of complications,
- patients have difficulty finding a pharmacy that stocks the drug because not all pharmacies may choose to stock the drug, resulting in treatment delay

Although not safety concerns, confidentiality and personal safety are significant concerns with Mifeprex. Distribution through retail pharmacies could compromise patient and

prescriber confidentiality with adding a new stakeholder to the treatment process, and pharmacies could be targeted by individuals or groups opposed to abortions.

Restriction of mifepristone to certain healthcare settings is probably the most critical element for maintaining confidentiality and privacy for both patients and prescribers. This element also contributes to the patient's safe use of Mifeprex by making the prescriber responsible for giving the drug directly to the patient and counseling the patient at the time of dispensing. It is safer for the patient - providing the opportunity for direct observed therapy (although this is not a REMS program requirement) to initiate the time-sensitive abortion process, and ensures the patient leaves the healthcare facility with the medications that are necessary for completing a medical abortion to maximize efficacy and minimize risk.

5.3 DOCUMENTATION OF SAFE USE CONDITIONS

The REMS requires that prescribers review and complete a Patient Agreement with each patient before treatment is initiated. The signed Agreement is placed in the patient's medical record; however it is not collected by Danco. There is no data available on how often the Agreement is utilized.

Family planning clinics generally utilize consent forms and in this type of practice setting the Patient Agreement may be redundant. Therefore, it is not known if removing this element would increase the risk that a patient is not properly informed and counseled about complications and what to do when a complication occurs.

6 DISCUSSION

(b) (6) and (b) (6) considered two options – maintain the REMS or eliminate the REMS with the following possible rationale for each option.

- Eliminate the REMS: No new safety concerns have been identified in 6 - 7 years. The serious complications being reported now have been consistent with labeling and the reporting rate has been stable over the last several years. These complications are consistent with what one would expect with a surgical abortion and are not necessarily unique to a medical abortion with Mifeprex. Use of Mifeprex has been primarily in Planned Parenthood and other family planning clinics where there are protocols and familiarity with assessing the duration of pregnancy, diagnosing an ectopic pregnancy, performing surgical interventions in cases of incomplete abortion, and caring for patients that experience serious complications. Some of the safe use practices surrounding Mifeprex may therefore already be embedded in these practice sites that already dispensing Mifeprex and would likely be maintained even if the REMS were eliminated.

- Maintain the REMS: There have been a small number of reported serious complications associated with Mifeprex and this is likely reflective of the use of Mifeprex within a system of knowledgeable healthcare providers, safe use protocols, proper patient counseling, and follow-up procedures.

  Medical abortion accounts for the minority of abortions in the U.S. Similarly, training opportunities in medical abortion appear limited and are less available than surgical abortion experience. Given this relative lack of familiarity and

experience with medical abortion, a restricted distribution program that reinforces the necessary skills and appropriate care (i.e., counseling and follow-up) is necessary to assuring safe use of Mifeprex.

The Mifeprex REMS provides the foundation to ensure the implementation of safe use conditions with Mifeprex use. Accurate gestation dating, patient education, dispensing Mifeprex directly to the patient during the office visit, and timely access to medical care remain important to maintaining the current safety profile of Mifeprex. It is not likely that the essential safe use conditions will be maintained to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events.

7 RECOMMENDATION AND CONCLUSION

(b) (6) recommends that the existing elements of the REMS should be maintained. Specifically, prescriber certification and dispensing limited to certain healthcare settings provide a framework to ensure that the benefits of Mifeprex outweigh its risks in an appropriate patient population.

On January 30, 2013, (b) (6) and (b) (6) presented this recommendation to the Center Director and senior level management from (b) (6) There was general consensus that a REMS is necessary to ensure that the benefits outweigh its risks.

Appendix A: Overview of US Mifeprex Cases with Fatal Outcomes

State	Date of Death	Patient Age	Cause of Death	Culture if Available
(b) (6)		38	Hemorrhage from ruptured ectopic pregnancy	N/A
		18	Septic shock	CDC positively identified *C. sordellii* in uterine tissue
		21	Presumed infection	CDC positively identified *C. sordellii* in uterine tissue
		22	Sepsis	CDC positively identified *C. sordellii* in uterine tissue
		34	Sepsis	CDC positively identified *C. sordellii* in uterine cavity
		32	Not specified^ (autopsy declined)	Uterine cavity culture positive for Prevotella and Peptostreptococcus
		23	Probably methadone overdose	N/A
		24	Septic shock	Probably *C. perfringens*
		22	Suspected homicide	N/A
		23	Cocaine and Fentanyl poisoning	N/A
		18	Septic shock & cardiac arrest	*C. sordellii* confirmed in uterine samples
		29	Complications due to acute endometritis & myometritis	CDC positively identified *C. sordellii* in uterine tissue
		21	Not specified, but presumed *C. sordellii infection*	CDC positively identified *C. sordellii*
		27	Ruptured ectopic pregnancy	N/A

[A]The (b) (6) death occurred on (b) (6) (Day 33) after an initial failed surgical and medical abortion on (b) (6) (Day 1) in a woman with a large uterine fibroid. A repeat surgical abortion was done on (b) (6) (Day 22). We do not believe the death was related to the attempted medical abortion on (b) (6).

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/s/

(b) (6)

10/17/2013

(b) (6)

10/17/2013

Received concurrence from (b) (6)

Exhibit I

2016 Mifeprex REMS Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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.

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/s/

(b) (6)

03/29/2016
adding to for the record

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

(b) (6)

(b) (6)

Date: March 29, 2016

(b) (6)

(b) (6) ((b) (6)

Subject: (b) (6) Assessment Review of the Year 4 risk evaluation and mitigation strategy (REMS) assessment report

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

This memo is to address specific statements made in the [redacted] ([redacted] Review of the Year 4 Risk Evaluation and Mitigation Strategy (REMS) assessment report that relate to an unapproved dosing regimen for Mifeprex.[1]

Mifeprex (NDA 20-687) is currently approved for the medical termination of intrauterine pregnancy through 49 days (7 weeks) gestation in a regimen with misoprostol. The currently approved dose of Mifeprex is 600 mg (three 200 mg) oral tablets which are to be taken under the supervision of a physician, followed two days later by two 200 mcg tablets (400 mcg) of misoprostol orally.

Danco Laboratories, LLC (Danco) submitted the 4 year REMS assessment report on June 2, 2015. The [redacted] REMS assessment reviewer had noted that there was use of the unapproved dosing regimen of Mifeprex 200 mg orally on day 1; followed by misoprostol 800 mcg, administered vaginally or buccally on day 3 or 4 for medical termination of intrauterine pregnancy up to 63 days gestation. The reviewer's comments included that it was unknown whether this unapproved regimen may have contributed to certain observed adverse events.

On May 29, 2015, Danco submitted a prior approval efficacy supplement-020 (PAS-020) seeking approval of certain changes to the approved indication, dosing regimen, and labeling for Mifeprex. Danco proposed to change the dosing regimen to: 200 mg orally x 1, instead of 600 mg orally x 1; followed 24-48 hours later by misoprostol 800 mcg, administered buccally; and an extension of gestational age from 49 to [redacted] 70 days). This supplement was under review at the time the October 2015 [redacted] REMS Assessment review was conducted.

The [redacted] ([redacted] is reviewing Danco's efficacy prior approval supplement-020 (PAS-020) to determine whether the supplement can be approved. Because [redacted] review encompasses all of the data and information submitted in the supplement, [redacted] defers to [redacted] with respect to the safety and efficacy of the dose and dosing regimen proposed by Danco.

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[1] [redacted] ([redacted] Review of Year 4 Risk Evaluation and Mitigation Strategy (REMS) Assessment Report, dated October 13, 2015

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/s/

(b) (6)

03/29/2016

memo to the assessment review

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.

b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber.

The above REMS modifications and changes in goals were discussed with the (b) (6) and concurrence with these changes was obtained.

The modified Mifeprex REMS should consist of ETASU A, in which healthcare providers who prescribe Mifeprex will be certified, and ETASU C, in which Mifeprex will be dispensed only in certain health care settings (specially clinics, medical offices, and hospitals) by or under the supervision of a certified prescriber. The Mifeprex REMS will also include an implementation system, and a timetable for continued submission of assessments of the REMS.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked (b) (6) and (b) (6) to continue to include a Patient Agreement form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through (b) (4), (b) (6) the Director, OSE, and (b) (6), to the Directors of (b) (6) and (b) (6) Therefore, the Patient Agreement form will be retained and other changes will be made in the REMS to reflect that it is being retained, as described in the (b) (6) Addendum to REMS Modification Review.

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/s/

(b) (6)

03/29/2016

Signing for (b) (6), (b) (6)

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

(b) (6)

(b) (6)

ADDENDUM TO REMS MODIFICATION REVIEW

Date:	March 29, 2016
Reviewer:	(b) (6) (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

1.

INTRODUCTION

This review is an addendum to the [redacted] March 29, 2016, REMS Modification Review regarding modifications to the risk evaluation and mitigation strategy (REMS) for Mifeprex, as proposed by Danco Laboratories in the amendment to the prior approval efficacy supplement 020 (PAS-20). See the March 29, 2016, REMS Modification Review for a description of the original submission and the existing REMS, and the materials informing our review.

In addition to those materials, we considered additional communications with the sponsor which included proposed changes to the REMS and REMS materials on March 21, 25, 27, 28 and 29th. We also considered a memorandum dated March 28, 2016 from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, requesting that [redacted] continue to include a Patient Agreement Form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through [redacted] This review addresses the sponsor's proposed changes as well as the changes that are needed in the REMS to reflect the fact that the Patient Agreement Form will be retained as part of the REMS.

This addendum will only describe changes that were recommended and that were not covered in the original REMS Modification Review. The changes we have agreed to were proposed to the sponsor and were accepted.

As with the original REMS modification review, all of the modifications discussed in this review were discussed with [redacted] and they are in agreement.

2. [redacted] AND SPONSOR PROPOSED MODIFICATIONS AND RATIONALE

2.1. REMS ELEMENTS

2.1.1. DOCUMENTATION OF SAFE USE CONDITIONS - ETASU D

2.1.1.1. PATIENT AGREEMENT FORM

As discussed above, it has been determined that the Mifeprex REMS should continue to include a Patient Agreement Form as ETASU D in the REMS. Therefore, the *Patient Agreement Form* is being revised as part of this modification.

The content has been modified to reflect the changes to the Prescribing Information that are being approved as part of the approval of PAS 020. These changes include changing the dosing regimen, updating the percentage of patients for which the treatment will not be effective, revising where Mifeprex or misoprostol should be taken and revising the patient follow-up recommendations after taking Mifeprex.

The requirement for a patient to read the MG has been removed since we are recommending that the MG be removed as an element of the REMS.[1] However, the MG will remain part of labeling

[1] [redacted] REMS Modification Review for Mifeprex, dated March 29, 2016.

and will still be required to be distributed to the patient as per 21 CFR part 208. In addition, certified HCPs will have agreed to provide a MG to the patient before providing Mifeprex.

Additionally, the reference to birth defects should be removed because the effects of Mifeprex on an ongoing pregnancy are unknown. Lastly, the attestation that the patient believes she is no more than a certain number of weeks pregnant should be removed. The Prescriber is responsible for accurately dating the pregnancy. Therefore, the patient should not be relied upon to date her own pregnancy.

2.2. REMS DOCUMENT

2.2.1. GOALS

As discussed in the REMS Modification Review dated March 29, 2016, the Mifeprex REMS goals should be modified. As discussed above, it has been determined that the Mifeprex REMS should continue to include the Patient Agreement Form, which is an ETASU D (documentation of safe use) requirement (see Section 4.1.1). Therefore, the goal of the REMS also should include objective c) below in underlined text.

> 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.
> b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber.
> c) Informing patients about the risk of serious complications associated with Mifeprex

(b) (4) The REMS goal should include the risks to be mitigated by the REMS. The phrase "risk of serious complications" was taken from the previously approved REMS document and continues to be applicable. (b) (6) recommends keeping the risks in the goal.

2.2.2. CERTIFICATION OF PRESCRIBERS - ETASU A

As discussed above, it has been determined that the Mifeprex REMS should continue to include the Patient Agreement Form. Therefore, ETASU A in the REMS document needs to be revised to reinsert information regarding this requirement. First, as was the case in the previously approved REMS document, certified prescribers must agree to review the Patient Agreement Form with the patient and answer any of her questions. Additionally, the prescriber must agree to sign the Patient Agreement Form and obtain the patient's signature on the form. Finally, the prescriber must agree to provide the patient with a copy of the Patient Agreement Form and insert a copy in the patient's chart. See redlined, attached REMS document.

In its March 21, 2016, submission, the Sponsor disagrees with changing the name of the *Prescriber's Agreement* to the *Prescriber Enrollment Form* because "enrollment" may be misconstrued by prescribers to mean they are being placed on a list or database. (b) (6) agrees

with the Sponsor's concern about using the term "Enrollment" in the title and proposes to change the name of the *Prescriber's Agreement* to the *Prescriber Agreement Form*. This has been reflected in the REMS document and the *Prescriber Agreement Form*.

The second proposed revision by the Sponsor applies to the qualifications of a certified prescriber. The REMS document currently states that prescribers must have the "ability to assess the duration of pregnancy accurately." Danco is proposing (b) (4) have concluded that not all practitioners are able to accurately assess gestational age. This ability is necessary for the safe use of Mifeprex.

In its March 21, 2016, submission, the Sponsor additionally proposed to insert "a non-identifiable reference" into the following statement in the REMS document and the *Prescriber Agreement Form* because it would increase the Sponsor's ability to track these adverse events. In addition, they stated that it is current practice for certified HCPs to provide this information. Danco also proposed removing "solely" from the statement, as shown below:

> Report any deaths to Danco Laboratories, identifying the patient ~~solely~~ by a non-identifiable reference and the serial number from each package of Mifeprex.

(b) (6) agreed with the above revisions. Lastly, the Sponsor proposed the following revised language in the REMS document and the Prescriber Agreement Form:

> …explain the risks (b) (4) of the ~~procedure, its effects, and the risks associated with~~ Mifeprex treatment regimen.

(b) (6) rejected the addition of (b) (4) to the REMS document and Prescriber Agreement Form. A REMS should only focus on the risks of a drug. Therefore, (b) (6) proposed that the final language be as follows:

> …explain the risks of the Mifeprex treatment regimen.

Additional minor edits and revisions were suggested for this section of the REMS document and corresponding language within the *Prescriber Agreement Form*. These changes were not intended to be substantive.

2.2.3. DOCUMENTATION OF SAFE USE CONDITIONS -ETASU D

As discussed above, it has been determined that the Mifeprex REMS should retain the Patient Agreement Form. Therefore, (b) (6) has proposed to insert the following text into the Mifeprex REMS document:

> 3. Mifeprex must be dispensed to patients with evidence or other documentation of safe use conditions.
>
> a. The patient must sign a *Patient Agreement Form* indicating that she has:
>
> i. Received, read and been provided a copy of the *Patient Agreement Form*.
>
> ii. Received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

2.2.4. IMPLEMENTATION SYSTEM

In its March 21, 2016, submission, the Sponsor proposed to [redacted] (b) (4)

a. Ship Mifeprex only to clinics, medical offices, and hospitals identified by certified prescribers in the signed *Prescriber Agreement Form*.

b. Complete the healthcare provider certification process upon receipt of the *Prescriber Enrollment Form*.

c. Notify healthcare providers when they have been certified by the Mifeprex REMS Program.

[redacted] (b) (6) [redacted] (b) (4). These are separate actions the distributor undertakes. Therefore, they should be described in the REMS document. Furthermore, it is not guaranteed that when a healthcare provider submits the *Prescriber Agreement Form*, they are ordering Mifeprex. In this situation, it is important that HCPs be notified when they are certified and, therefore, able to order Mifeprex in the future.

Lastly, [redacted] (b) (6) proposed to move the adverse event reporting requirements from the assessment to the implementation system of the REMS and to remove the requirement to report certain specifically enumerated adverse events such as all hospitalizations due to complications and women requiring transfusions, but retain the requirement to report all deaths. The following language was inserted:

"Danco Laboratories must report to FDA any death associated with Mifeprex whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under the FDA regulations."

3. CONCLUSION

The review team and Sponsor have proposed additional modifications that continue to ensure that the benefit outweighs the risk for Mifeprex. This addendum addresses modifications to the REMS including those proposed by the sponsor in its March 21, 25, 27, 28 and 29, 2016, submissions, and additional changes recommended by [redacted] (b) (6) The additional changes include the following: reinsertion of the Prescriber Agreement Form (ETASU D) with certain changes to other documents to reflect this, and modification of the REMS goal, REMS document and appended materials provided to the Sponsor on March 17, 2016.

As discussed above, several changes to the language in the REMS document were proposed by Danco. The [redacted] (b) (4) were rejected by [redacted] (b) (6) The Sponsor additionally expressed their desire to not change the name of the *Prescriber's Agreement* to the *Prescriber Enrollment Form,* as suggested by the review team. In consideration of this, [redacted] (b) (6) proposes to change the title to the *Prescriber Agreement Form.*

The above changes to the REMS document and materials are appropriate modifications to the Mifeprex REMS. They are necessary to ensure that that the risks of serious complications will be mitigated and that the benefits of Mifeprex will continue to outweigh the risks.

4. RECOMMENDATIONS

The proposed amended modification submitted by Danco on March 29, 2016 is acceptable and (b) (6) recommends approval of the REMS.

Appendix

1. Prescriber Enrollment Form, clean
2. Patient Agreement Form, clean
3. REMS Document, clean

Initial REMS approval: 06/2011
Most recent modification: 03/2016

NDA 020687 MIFEPREX® (mifepristone) Tablets, 200 mg

Antiprogestational Synthetic Steroid

Danco Laboratories, LLC
PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

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.

b) Ensuring that Mifeprex is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber.

c) Informing patients about the risk of serious complications associated with Mifeprex

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe Mifeprex must be specially certified.

   a. To become specially certified to prescribe Mifeprex, healthcare providers must:

      i. Review the Prescribing Information for Mifeprex.

      ii. Complete the *Prescriber Agreement Form*. By signing the *Prescriber Agreement Form*, prescribers agree that:

         1) They have the following qualifications:

            a) Ability to assess the duration of pregnancy accurately

b) Ability to diagnose ectopic pregnancies
c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

2) They will follow the guidelines for use of Mifeprex (see b.i-v below).

b. As a condition of certification, healthcare providers must follow the guidelines for use of Mifeprex described below:

i. Review the *Patient Agreement Form* with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
ii. Sign the *Patient Agreement Form* and obtain the Patient's signature on the *Form*
iii. Provide the patient with a copy of the *Patient Agreement Form* and Medication Guide.
iv. Place the signed *Patient Agreement Form* in the patient's medical record.
v. Record the serial number from each package of Mifeprex in each patient's record.
vi. Report any deaths to Danco Laboratories, identifying the patient by a non-identifiable reference and the serial number from each package of Mifeprex.

c. Danco Laboratories must:

i. Ensure that healthcare providers who prescribe Mifeprex are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements
ii. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *Prescriber Agreement Form*
- *Patient Agreement Form*

2. Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

a. Danco Laboratories must:

i. Ensure that Mifeprex is available to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber.

ii. Ensure that Mifeprex is not distributed to or dispensed through retail pharmacies or other settings not described above.

3. Mifeprex must be dispensed to patients with evidence or other documentation of safe use conditions.
   a. The patient must sign a *Patient Agreement Form* indicating that she has:
      i. Received, read and been provided a copy of the *Patient Agreement Form*.
      ii. Received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

B. Implementation System

1. Danco Laboratories must ensure that Mifeprex is only distributed to clinics, medical offices and hospitals by or under the supervision of a certified prescriber by:

   a. Ensuring that distributors who distribute Mifeprex comply with the program requirements for distributors. The distributors must:

      i. Put processes and procedures in place to:

         a. Complete the healthcare provider certification process upon receipt of the *Prescriber Agreement Form.*

         b. Notify healthcare providers when they have been certified by the Mifeprex REMS Program.

         c. Ship Mifeprex only to clinics, medical offices, and hospitals identified by certified prescribers in the signed *Prescriber Agreement Form*.

         d. Not ship Mifeprex to prescribers who become de-certified from the Mifeprex Program.

         e. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who (1) attempt to order Mifeprex and are not yet certified, or (2) inquire about how to become certified.

      ii. Put processes and procedures in place to maintain a distribution system that is secure, confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of Mifeprex.

      iii. Train all relevant staff on the Mifeprex REMS Program requirements.

      iv. Comply with audits by Danco Laboratories, FDA or a third party acting on behalf of Danco Laboratories or FDA to ensure that all processes and procedures are in place and are being followed for the Mifeprex REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

   b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of Mifeprex.

2. Danco Laboratories must monitor distribution data to ensure compliance with the REMS Program.

3. Danco Laboratories must audit new distributors within 90 calendar days after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifeprex REMS Program. Danco Laboratories will take steps to address distributor compliance if noncompliance is identified.

4. Danco Laboratories must take reasonable steps to improve implementation of and compliance with the requirements of the Mifeprex REMS Program based on monitoring and assessment of the Mifeprex REMS Program.

5. Danco Laboratories must report to FDA any death associated with Mifeprex whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

Danco Laboratories must submit REMS assessments to FDA one year from the date of the initial approval of the REMS (06/08/2011) and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco Laboratories must submit each assessment so that it will be received by the FDA on or before the due date.

APPEARS THIS WAY ON ORIGINAL

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To set up your account to receive Mifeprex, you must:
1. complete, 2. sign, and 3. fax page 2 of this form to the distributor.

If you will be ordering for more than one facility, you will need to list each facility on your order form before the first order will be shipped to the facility.

Prescriber Agreement: By signing page 2 of this form, you agree that you meet the qualifications below and will follow the guidelines for use. You also understand that if you do not follow the guidelines, the distributor may stop shipping Mifeprex to you.

Mifeprex must be provided by or under the supervision of a healthcare provider who prescribes and meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of Mifeprex. The Prescribing Information is available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Review the Patient Agreement Form with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of Mifeprex in each patient's record.
- Report deaths to Danco Laboratories, identifying the patient by a non-identifiable patient reference and the serial number from each package of Mifeprex.

ACCOUNT SETUP MIFEPREX® (Mifepristone) Tablets, 200 mg; NDC 64875-001-01

TO SET UP YOUR ACCOUNT:

1. Read the Prescriber Agreement on page 1 of this form.
2. Complete and sign this form.
3. Fax this page to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned or faxed and are usually shipped within 24 hours.

Mifeprex® (Mifepristone) Tablets, 200 mg
THE ORIGINAL EARLY OPTION PILL

BILLING INFORMATION

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

SHIPPING INFORMATION ☐ *Check if same as above*

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

ADDITIONAL SITE LOCATIONS *I will also be prescribing Mifeprex* at these additional locations:*

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

REQUEST ADDITIONAL MATERIALS

☐ **Medication Guides** ☐ **State Abortion Guides** ☐ **Patient Brochures** ☐ **Patient Agreement Form**

ESTABLISHING YOUR ACCOUNT *(required only with first order)*

Each facility purchasing Mifeprex must be included on this form (*see additional site locations box above*) before the distributor can ship the product to the facility.

By signing below, you agree that you meet the qualifications and that you will follow the guidelines for use on page 1 of the Prescriber Agreement.

Print Name _____ Signature _____

Medical License # _____ Date _____

FAX THIS COMPLETED FORM TO THE AUTHORIZED DISTRIBUTOR. FAX: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

PATIENT AGREEMENT FORM

Mifeprex® (Mifepristone) Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of Mifeprex*. Both you and the patient must sign this form.*

Patient Agreement:

1. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take Mifeprex on Day 1.
   b. My provider will either give me or prescribe for me the misoprostol tablets which I will take 24 to 48 hours after I take Mifeprex.
3. My healthcare provider has talked with me about the risks including:
   - heavy bleeding
   - infection
   - ectopic pregnancy (a pregnancy outside the womb)
4. I will contact the clinic/office right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - severe stomach area (abdominal) pain
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - stomach pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
5. My healthcare provider has told me that these symptoms could require emergency care. If I cannot reach the clinic or office right away my healthcare provider has told me who to call and what to do.
6. I should follow up with my healthcare provider about 7 to 14 days after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
7. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
8. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
9. I have the MEDICATION GUIDE for Mifeprex. I will take it with me if I visit an emergency room or a healthcare provider who did not give me Mifeprex so that they will understand that I am having a medical abortion with Mifeprex.
10. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name (print):** _____ **Date:** _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for Mifeprex.

Provider's Signature: _____ **Name of Provider (print):** _____ **Date:** _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record.

03/2016

Reference ID: 3909588

DANCO

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

/s/

(b) (6)

03/29/2016

(b) (6)

03/29/2016

Concur

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

Table of Contents

1. INTRODUCTION

This review provides the (b) (6) (b) (6) evaluation of the modifications to the risk evaluation and mitigation strategy (REMS) for Mifeprex proposed in the efficacy supplement submitted by Danco Laboratories (Danco) on May 29, 2015, and provides (b) (6) recommendations to the (b) (6) (b) (6) The approved REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The evaluation of modifications to the approved REMS utilized input received from the (b) (6) (b) (6) [1], REMS assessment data, and a postmarketing summary report by the (b) (6) (b) (6)

1.1 BACKGROUND

Mifeprex is a synthetic steroid with antiprogestational effects. The currently approved dose is three 200 mg oral tablets which are to be taken under the supervision of a physician for the medical termination of intrauterine pregnancy through 49 days gestation. Mifeprex was approved September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (Subpart H).[2] Mifeprex was deemed to have a 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. A formal REMS proposal was submitted by Danco and approved on June 8, 2011with a MG, ETASU, an implementation system and a timetable for submission of assessments. The goals and elements of the REMS are briefly summarized in Table 1 below.

Table 1. Summary of Currently Approved Mifeprex REMS

REMS Goals	To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.

[1] (b) (6)

[2] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

	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 dispensed only in certain healthcare settings: It is only available to be dispensed in clinics, medical offices or hospitals, by or 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's Agreement form that is to be placed in the patient's medical record. A copy of the Patient's Agreement form and MG 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.

1.2 Brief Summary of Key Regulatory History

A brief summary of the key regulatory history relevant to the Mifeprex REMS is listed below:

September 28, 2000: Mifeprex is approved with restricted distribution and postmarketing commitments under 21 CFR 314.520 (Subpart H).

September 27, 2007: FDAAA enacted and Mifeprex is deemed to have a REMS.

June 8, 2011: Mifeprex REMS is approved, NDA 020687/S-014

June 1, 2012: REMS Assessment Report, Year 1

June 2, 2015: REMS Assessment Report, Years 2-4

May 29, 2015: Danco submitted PAS- 020 efficacy supplement

January 15, 2016: A (b) (6) meeting was held to discuss proposed revisions to the REMS which included revising the REMS goal and removal of the MG and Patient Agreement form as elements of the REMS.

2. MATERIALS REVIEWED

2.1 SUBMISSIONS

- Danco Laboratories, Prior Approval Efficacy Supplement and REMS Modification, PAS-020, received May 29, 2015 (paper submission)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Mifeprex approval letter, dated September 28, 2000
- (b) (6) Mifeprex PAS-014 approval letter, dated June 8, 2011
- (b) (6) Final deemed REMS Review for Mifeprex:, dated June 3, 2011
- (b) (6) Review of Year 1 REMS Assessment Report: dated August 1, 2012
- (b) (6) Review of Year 4 REMS Assessment Report: dated October 13, 2015

- (b) (6) Mifeprex Post-marketing Safety Review: dated August 20, 2015
- Addendum to (b) (6) Review of Year 4 REMS Assessment Report: dated March 29, 2016
- (b) (6) draft Clinical Review for Mifeprex, NDA 020687, PAS 20: dated March 29, 2016.

3. OVERVIEW OF RATIONALE FOR PROPOSED REMS MODIFICATIONS

On May 29, 2015, Danco submitted an efficacy prior approval supplement-020 (PAS-020) and REMS modification. In PAS-020, Danco is seeking approval of certain changes, including:

- Dosing of 200 mg orally x 1, instead of 600 mg orally x 1
- Extension of maximum gestational age
- Inclusion of misoprostol in the indication statement
- Inclusion of information regarding Pediatric Research Equity Act (PREA) data
- Replacement of the term "physician" with "(b) (4) in the PI and the REMS Prescriber's Agreement
- Removal of the phrase "Under Federal Law" from the REMS Prescriber's Agreement
- Revisions to the Patient Agreement Form to reflect proposed changes in the PI

The Sponsor's proposed changes in the efficacy supplement prompted revisions to the Mifeprex REMS materials. During review of the efficacy supplement and proposed REMS Modifications, (b) (6) evaluated the current REMS program to determine whether other changes were appropriate. As part of this evaluation, the review team took into consideration the recent (b) (6) review of the Mifeprex REMS Assessment completed on October 13, 2015, the addendum to the October 13, 2015 review completed on March 29, 2016, safety data gathered over the past 16 years since approval, and information regarding current clinical practice.[5,6,8,9]

Based on the available data and information, (b) (6) continues to believe that a REMS is necessary to ensure the benefits outweigh the risks; however, we recommend that some elements be modified or removed. All of the modifications in this review were discussed with (b) (6) The recommended modifications and supporting rationale for each are further described in Sections 4 and 5 below.

4. SPONSOR PROPOSED MODIFICATIONS AND RATIONALE

4.1. REMS ELEMENTS

4.1.1. CERTIFICATION OF PRESCRIBERS - ETASU A

4.1.1.1. PRESCRIBER'S AGREEMENT

Danco is proposing two modifications to the Prescriber's Agreement form. The first proposal is to remove the phrase "Under Federal law" from the document. This phrase appears twice in the Prescriber's Agreement:

(1) *Under Federal law*, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications…
(2) *Under Federal law*, each patient must be provided with a Medication Guide.

The Sponsor is proposing that the phrase be deleted from the beginning of the above sentences to be consistent with current REMS language.

Reviewer Comment: The review team agrees with this revision. The review team has determined that there is no precedent in other REMS for using the phrase, nor is there any clinical rationale for including it. As approvals are governed by Federal law, the review team concludes that the phrase "Under Federal law" is unnecessary in the Prescriber's Agreement.

The second proposed modification from Danco is to replace the word "physician" with "(b) (4) The Prescriber's Agreement currently reads: "Under Federal law, Mifeprex must be provided by or under the supervision of a *physician* who meets the following qualifications…" The Sponsor is proposing that the agreement read: "Mifeprex must be provided by or under the supervision of a (b) (4) who meets the following qualifications…"

Reviewer Comment: The review team agrees that the term "physician" should be replaced, but with the phrase "healthcare provider who prescribes." '(b) (4) . Mifeprex is a prescription medication and "healthcare providers who prescribe" accurately describes not only physicians but other healthcare providers, for example, nurse practitioners, certified nurse midwives and physician assistants, who may prescribe medications. Additionally, the phrase "healthcare provider who prescribes" is consistent with the language that is included in the statute.[3]

5. (b) (6) PROPOSED MODIFICATIONS AND RATIONALE

5.1. REMS ELEMENTS

5.1.1. MEDICATION GUIDE

FDA has generally been maintaining MGs as FDA-approved labeling but removing them from REMS when inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks. The Mifeprex MG, though an important tool for patient education that will continue to be distributed to patients, does not need to be an element of the REMS to ensure the benefits outweigh the risks for Mifeprex. The MG will remain part of labeling and will still be required to be distributed to the patient as per 21 CFR part 208. This approach is consistent with ongoing efforts to streamline REMS by allowing for changes to a MG without the need for a REMS modification.

5.1.2. CERTIFICATION OF PRESCRIBERS - ETASU A

5.1.2.1. PRESCRIBER'S AGREEMENT

Per the current Mifeprex REMS, a Prescriber's Agreement is required to be completed, signed and faxed to the distributor to complete enrollment. The review team is recommending

[3] FDCA 505-1(f)(3)(A).

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

[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

"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.
b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber."

5.2.2. MEDICATION GUIDE

(b) (6) recommends this element be removed from the REMS document. See Section 5.1.1 for rationale.

5.2.3. CERTIFICATION OF PRESCRIBERS - ETASU A

The language in the REMS document stating that certified prescribers must obtain a completed Patient Agreement form from the patient is recommended to be removed (see Section 5.1.2.1 for rationale). In addition, edits to align the REMS document with language in the revised PI are being made. Finally, we recommend that this section of the REMS document be revised and edited to reflect the Agency's current thinking on the most appropriate language and flow of REMS documents. However, the requirement for Prescriber Certification remains and the qualifications of a healthcare provider who prescribes Mifeprex have not changed and continue to be necessary to ensure the benefits outweigh the risks.

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

This section of the REMS was edited to provide clarification on where Mifeprex will not be dispensed.

In addition, the REMS document was revised and edited to reflect (b) (6) current thinking on the language and flow of REMS documents. These changes are not intended to be substantive.

5.2.5. DOCUMENTATION OF SAFE USE CONDITIONS -ETASU D

This element is being recommended for removal from the REMS document. See section 5.1.4.1 for rationale.

5.2.6. IMPLEMENTATION SYSTEM

This section of the REMS document is proposed to be revised and edited to reflect the Agency's current thinking on the language and flow of REMS documents.

5.2.7. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

This section of the REMS document is proposed to be revised and edited to reflect the Agency's current thinking on the language and flow of REMS documents.

5.3. ASSESSMENT PLAN

Currently, the REMS Assessment Plan requires Danco to submit the following adverse event information as part of the periodic REMS Assessment Report:

> 6. Copies of MedWatch forms for each of the following adverse events during the assessment period; and for each of the following adverse events, the cumulative number from the date of approval of Mifeprex up to the approval date of the REMS, the number for each reporting period, and the cumulative number since the approval date of Mifeprex:
>
> a. On-going pregnancies not terminated subsequent to the conclusion of the treatment procedure
> b. Women hospitalized due to complications
> c. Women requiring transfusion(s) of two or more units of packed cells or whole blood, or having a hemoglobin of 6 gm/dL or less or a hematocrit of 18% or less
> d. Serious infection, sepsis
> e. Death
> f. Other serious and unexpected adverse events
>
> 7. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue.

This information is being submitted to the Agency through other pathways including spontaneous adverse event reporting and the annual report. Therefore, (b) (6) is recommending it be removed from the Assessment Plan.

The revised Assessment Plan is as follows:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative)
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

6. CONCLUSION

A REMS for Mifeprex is necessary to ensure that the benefits outweigh the risks. The review team and Sponsor have proposed modifications that continue to ensure that the benefit outweighs the risk, while updating the REMS in light of current medical practice and to provide clarifying language in the REMS documents.

The modifications to the Mifeprex REMS include the sponsor's proposed modifications and additional changes recommended by the review team and include the following: revision of the REMS goals, removal of the MG (it will remain as part of labeling) and the Patient Agreement; and changes to the Prescriber Enrollment Form.

7. RECOMMENDATIONS

(b) (6) recommends the changes in the attached, redlined REMS document and materials, which represent (b) (6) proposed changes to the REMS as a result of this REMS Modification Review.

8. APPENDIX

1. Prescriber Enrollment Form, redlined
2. Prescriber Enrollment Form, clean
3. REMS Document, redlined
4. REMS Document, clean

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

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