

**UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF MISSISSIPPI
NORTHERN DIVISION**

GENBIOPRO, INC.

PLAINTIFF

V.

CIVIL ACTION NO. 3:20-CV-00652-HTW-LGI

**DR. THOMAS DOBBS, STATE HEALTH OFFICER
OF THE MISSISSIPPI DEPARTMENT OF HEALTH,
IN HIS OFFICIAL CAPACITY**

DEFENDANTS

[PROPOSED] AMENDED COMPLAINT

Plaintiff GenBioPro, Inc. (“GBP”), by its undersigned counsel, hereby brings this Complaint against Defendant Dr. Thomas Dobbs, State Health Officer of the Mississippi Department of Health, in his official capacity and states and alleges as follows:

I. INTRODUCTION

1. Mississippi’s laws restricting the use of the Food and Drug Administration’s (“FDA”) approved drug mifepristone conflict with federal law and are therefore preempted. The FDA, after exhaustive review and re-review, balanced patient safety and access in approving use of mifepristone for termination of early pregnancies, subject to a risk management plan known as a Risk Evaluation and Mitigation Strategy, or “REMS.” First approved as a safe and effective medication in 2000 (with GBP’s generic version approved in April 2019), the FDA has reiterated that adverse events associated with mifepristone are “exceedingly rare,” and the drug is safer than either continuing a pregnancy (which can cause any number of health issues) or other methods for terminating an unwanted pregnancy.

2. As mandated by Congress, the FDA considered whether there were any patient risks that should be mitigated through use of a REMS. This consideration includes ensuring that any



REMS restrictions “not be unduly burdensome on patient access to the drug, considering in particular . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)” and should be designed to “minimize the burden on the health care delivery system[.]” Federal Food, Drug & Cosmetic Act of 1938 (“FDCA”), 21 U.S.C. § 355-1(f)(2)(C), (C)(ii), (D); 21 U.S.C. § 301. Under that express authority granted by Congress, the FDA imposed restrictions on who can prescribe mifepristone, where it can be dispensed, and what information must be given to patients – all to ensure patient safety without unduly burdening access.

3. Contrary to these federal authorities, Mississippi has instituted a near-total ban on medicated abortion and, in the rare circumstance in which medicated abortion is available, has imposed a number of *additional* requirements before mifepristone can be dispensed in the state. The ban and restrictions effectively preclude GBP from operating in Mississippi. By obstructing GBP’s ability to provide and patients’ ability to obtain mifepristone, Mississippi’s laws contravene not only the FDA’s approval of mifepristone, but the FDA’s judgment concerning the safety and efficacy of mifepristone and how best to ensure patient access to mifepristone. As an example, under the FDA’s regimen, a woman can receive mifepristone from a nurse practitioner (with certain qualifications), and then take the medication in the privacy and comfort of her own home, following up with her health care provider 7 to 14 days later (which need not be an in-person visit). By contrast, that same woman in Mississippi is entirely prevented from receiving mifepristone, except in the few cases where her life is at stake or where the pregnancy was caused by rape and the woman has filed a formal rape charge. And, even in those limited circumstances, the Mississippi woman would need to have an initial counseling and ultrasound appointment in-person with a physician, followed by a 24-hour wait before she may receive mifepristone. At the

second visit, the patient must physically ingest the mifepristone in the physician's presence, and then return again to see that physician 7 to 14 days later. Such dramatic curtailment of access to an FDA-approved medication contravenes federal law, and is thus unconstitutional under the Supremacy Clause of the United States Constitution, and is preempted.

4. By this action, GBP seeks to provide the women of Mississippi with access to mifepristone as permitted by federal law, through permanent injunctive relief and declaratory judgment setting aside as unconstitutional Mississippi's laws and regulations that prevent or restrict the administration of a drug approved by the FDA as safe and effective when used in accordance with the FDA's approved label and REMS.

II. JURISDICTION AND VENUE

5. Jurisdiction is proper under 28 U.S.C. § 1331 because this action arises under the laws of the United States, and 28 U.S.C. § 2201 in that there exists between GBP and the Defendant an actual, justiciable controversy as to which GBP requires a declaration of its rights by this Court as well as permanent injunctive relief to prohibit the Defendant from violating federal laws and regulations protected under the United States Constitution.

6. Venue is proper in the Southern District of Mississippi pursuant to 28 U.S.C. § 1391(b) because a substantial part of the events or omissions giving rise to this action occurred in the District, including Defendant's decision to implement the policies at issue in this action and because, upon information and belief, Defendant is located in this judicial district.

7. GBP has standing to bring the present lawsuit because Defendant's actions effectively prevent GBP from selling its product in Mississippi and have caused GBP actual injury, which is redressable through the specific relief requested herein. As a pharmaceutical company marketing and selling mifepristone through interstate commerce pursuant to its approval by the

FDA, GBP's operations fall within the zone of interests to be protected by the dormant Commerce Clause of the United States Constitution, as well as general federal preemption principles.

8. This case is ripe for adjudication. As further discussed below, the enforcement of Mississippi's restrictions on the prescription and provision of mifepristone results in an ongoing and concrete invasion of GBP's legally protected interests under federal law.

9. This Court has authority to grant declaratory and injunctive relief pursuant to 28 U.S.C. §§ 2201–2202, and the inherent equitable powers of this Court.

10. There exists an actual and justiciable controversy between Plaintiff and Defendant requiring resolution by this Court. Plaintiff has no adequate remedy at law.

III. PARTIES

11. **Plaintiff GenBioPro, Inc.** is a Nevada corporation with its principal place of business located at 651 Lindell Road, Suite D1041 (P.O. Box 32011), Las Vegas, Nevada, 89103. GBP markets and sells generic mifepristone—a drug that blocks the hormone progesterone, which is needed for a pregnancy to continue—for which it holds an approved Abbreviated New Drug Application, No. 091178.

12. **Defendant Thomas E. Dobbs III, M.D., M.P.H.**, is the State Health Officer of the Mississippi Department of Health. Dr. Dobbs maintains an office at the Mississippi State Department of Health Central Office, 570 East Woodrow Wilson Drive, O-400, Jackson, Mississippi, 39216. Dr. Dobbs is responsible for supervising and directing all activities of the Mississippi State Department of Health. MISS. CODE ANN. §§ 41-3-5.1, 41-3-15(1)(a), (c). Such activities include the licensing and regulating of abortion facilities in accordance with Mississippi law. *Id.* § 41-75-1. Dr. Dobbs is being sued in his official capacity.

IV. THE NATURE OF THE CASE

A. What is Mifepristone?

13. The current FDA-approved regimen for the medical termination of early pregnancy involves two medications: (1) *mifepristone*, which interrupts early pregnancy by blocking the effect of progesterone, a hormone necessary to maintain a pregnancy, and (2) *misoprostol*, which causes uterine contractions that expel the pregnancy from the uterus.¹ The FDA has approved the use of this regimen through 70 days of pregnancy with specific labeling and approved conditions of use under both the labeling and mifepristone REMS program.

14. Mifepristone was first approved for the medical termination of early pregnancy in France and China in 1988, in the United Kingdom in 1991, in Sweden in 1992, and in numerous other European countries throughout the 1990s. In 1996, a new drug application (“NDA”) was sponsored for mifepristone in the United States under the brand name Mifeprex, for use in combination with misoprostol for the medical termination of early pregnancy. The FDA approved the NDA in 2000 and Danco Laboratories, L.L.C. (“Danco”) began marketing and selling Mifeprex in the United States in November of that year.

15. Plaintiff GBP submitted an abbreviated new drug application (“ANDA”) for its product, Mifepristone tablets, a generic version of Mifeprex, to the FDA on February 3, 2009. The FDA approved GBP’s ANDA on April 11, 2019.²

¹ U.S. FOOD & DRUG ADMIN., *Mifeprex (mifepristone) Information* (Dec. 16, 2021) [hereinafter *Mifeprex (mifepristone) Information*], <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/mifeprex-mifepristone-information>.

² U.S. FOOD & DRUG ADMIN., *ANDA Approval Letter for Mifepristone Tablets, 200 mg, ANDA No. 091178* (Apr. 11, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2019/091178Orig1s000ltr.pdf.

16. Mifepristone is currently the only medication approved in the United States for the medical termination of a pregnancy. Plaintiff's Mifepristone tablets are the only FDA-approved generic version of the medication for this indication.

B. The Federal Regulatory Scheme for Prescription Drugs

1. The United States Food and Drug Administration's Authority to Regulate Prescription Drugs

17. Congress has granted the FDA, through the FDCA, the authority to assess the safety and efficacy of prescription drugs, balance the risks and benefits of drug therapies to the public health, and approve them for marketing and sale in the United States. 21 U.S.C., ch. 9. The FDA approves prescription drugs and determines appropriate conditions for their safe and effective use after conducting a comprehensive and thorough review of available scientific evidence and carefully balancing the risks and benefits to public safety.

18. The FDA's federally-mandated role is to assess the benefits of a proposed drug alongside its risks, approving only those drugs that strike an appropriate balance between the two, while providing the best guidance to healthcare providers and patients on the safety precautions and risks of a drug to ensure its safe and effective use. This

[b]enefit-risk assessment is an integral part of [the] FDA's regulatory review of marketing applications for new drugs and biologics. These assessments capture the Agency's evidence, uncertainties, and reasoning used to arrive at its final determination for specific regulatory decisions.³

19. In assessing and approving prescription drugs for sale and marketing in the United States, the FDA's role is not simply to rubber stamp requests for drug approvals. Rather, the FDA conducts a comprehensive and holistic assessment, weighing the risks and benefits of certain drugs

³ U.S. FOOD & DRUG ADMIN., *Enhancing Benefit-Risk Assessment in Regulatory Decision-Making* (July 15, 2022), <https://www.fda.gov/industry/prescription-drug-user-fee-amendments/enhancing-benefit-risk-assessment-regulatory-decision-making>.

and other medical technologies in order to strike the right balance between access to drug therapies on the one hand and the public’s safety on the other. Carefully and comprehensively weighing the risks of a drug and crafting a detailed risk mitigation plan, when necessary, is the key to achieving the balance at the heart of the FDA’s public health mission.

20. Congress has also given the FDA additional powers to place extra protections around the administration of certain drugs to ensure patient safety when necessary. In 2007, the FDCA was amended to establish the FDA’s authority to impose a REMS, a “required risk management plan that can include one or more elements to ensure that the benefits of a drug outweigh its risks.”⁴ The REMS statutory scheme is discussed further below. *Infra* Sections IV.B.3–4.

2. The FDA’s Extensive Approval Process for New Drugs

21. Congress has vested the FDA with responsibility for reviewing and approving all new prescription drugs (and their generic equivalents) sold in the United States. To that end, the FDCA requires all new prescription drugs to obtain FDA approval under an NDA before they can enter the marketplace. 21 U.S.C. § 355(a), (b).

22. To receive approval, drug manufacturers must provide extensive evidence that their drug is safe and effective. *See* 21 U.S.C. § 355(b). To establish safety and effectiveness, an NDA must include “full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use[.]” *Id.* § 355(b)(1).

23. Upon receipt of an NDA, the FDA is charged with performing a thorough analysis of the drug’s safety and effectiveness—a process that requires the agency to carefully balance the

⁴ U.S. DEP’T OF HEALTH & HUM. SERVS. & U.S. FOOD & DRUG ADMIN., *REMS: FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary: Guidance for Industry 2* (Apr. 2019), <https://www.fda.gov/media/100307/download> (footnote omitted).

benefits and risks to patients. 21 U.S.C. § 355(c), (d). The FDA will approve an NDA only when all necessary data are submitted or referenced to establish the product’s safety and effectiveness.

Id. And the FDA will refuse to approve an NDA if it finds that the application and the data presented to support the application do not establish the safety and effectiveness of the product.

Id. § 355(d); Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.125.

24. All drugs have some ability to cause adverse effects. Thus, the FDA’s safety assessment of a drug is determined by whether its benefits outweigh its risks. As the FDA notes, “[b]enefit-risk assessment is the foundation for [the] FDA’s regulatory review of human drugs and biologics,”⁵ and this assessment is made after careful and comprehensive review process:

[F]or a drug to be approved for marketing, FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. This assessment is informed by an extensive body of evidence about the drug’s safety and efficacy submitted by an applicant in a . . . (NDA) or Biologics Licensing Application (BLA). This assessment is also informed by a number of other factors, including: the severity of the underlying condition and how well patients’ medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the postmarket setting; and whether risk management tools are necessary to manage specific risks.⁶

25. As a part of its assessment, the FDA considers “[s]trategies for managing risks[,]” which include “an FDA-approved drug label . . . describ[ing] the drug’s benefits and risks, and how the risks can be detected and managed. [For some drugs], more effort is needed to manage risks. In these cases, a drug maker may need to implement a . . . (REMS).”⁷

⁵ U.S. FOOD & DRUG ADMIN., *Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA VI Implementation Plan (FY 2018–2020)* 2 (Mar. 30, 2018), <https://www.fda.gov/media/112570/download> (footnote omitted).

⁶ *Id.* at 3.

⁷ U.S. FOOD & DRUG ADMIN., *Development & Approval Process | Drugs* (Apr. 8, 2022), <https://www.fda.gov/drugs/developmentApprovalProcess/default.htm>.

26. Based on this review, the FDA either: (1) approves the drug; (2) informs the sponsor that the drug is likely to be approved once certain deficiencies in the NDA are resolved; or (3) indicates that approval cannot be obtained without substantial additional data.

27. The FDA follows a similar process in evaluating a supplemental NDA, in which a drug sponsor requests approval to make changes to the label of a previously approved drug or to market the drug for a new indication, as was done for mifepristone in 2016.

28. Under the 1984 Hatch–Waxman Amendments to the FDCA, a company wishing to market the generic version of a previously approved drug may bypass the burdensome NDA process and obtain FDA approval to market the generic version by submitting an ANDA. 21 U.S.C. § 355(j)(2)(A). The ANDA process provides for the approval of a generic drug if the applicant can show its product’s “bioequivalence” to the earlier-approved NDA drug and show that its product meets both applicable product specifications and quality requirements, without repeating the clinical efficacy studies required for the initial NDA approval.⁸ 21 U.S.C. § 355(j)(8).

3. The Risk Evaluation and Mitigation Strategy Statute

29. In 2007, when Congress amended the FDCA with the FDA Amendments Act, Pub. L. No. 110-85, 121 Stat. 823 (2007), it added a new section, 505-1 (codified as amended at 21 U.S.C. § 355-1), authorizing the Secretary of Health and Human Services (“HHS”), in consultation with the FDA’s Office of New Drugs and the Office of Surveillance and Epidemiology, to impose a REMS if “necessary to ensure that the benefits of the drug outweigh [its] risks” 21 U.S.C.

⁸ At its most simply stated, bioequivalence means that the drug is comparable in “dosage form, strength, route of administration, quality, performance characteristics, and intended use” as the NDA drug. U.S. FOOD & DRUG ADMIN., *Abbreviated New Drug Application (ANDA)* (Jan. 14, 2022), <https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda>.

§ 355-1(a)(1). Congress mandated clear and complete authority to the HHS Secretary to ensure FDA appropriately balances a drug’s benefits against its “serious risks” when imposing REMS requirements. *Id.*

30. To determine whether a REMS is necessary, the Secretary must consider six factors: (1) “[t]he estimated size of the population likely to use the drug involved,” (2) “[t]he seriousness of the disease or condition that is to be treated with the drug,” (3) “[t]he expected benefit of the drug with respect to such disease or condition,” (4) “[t]he expected or actual duration of treatment with the drug,” (5) “[t]he seriousness of any known or potential adverse events that may be related to the drug and the background incidence [*i.e.*, frequency] of such events in the population likely to use the drug,” and (6) “[w]hether the drug is a new molecular entity.” 21 U.S.C. § 355-1(a)(1)(A)–(F).

31. A REMS may include any or all of the following: a medication guide and/or patient package insert; a communication plan; and elements to assure safe usage (*i.e.*, “ETASU”), such as a restricted distribution scheme or special requirements for the administration of the drug. 21 U.S.C. § 355-1(e)–(f).

32. ETASU are the most restrictive and burdensome type of REMS. Congress imposed several additional requirements to ensure that, even for drugs requiring ETASU, the FDA appropriately balances such a drug’s benefits against its “serious risks.” The ETASU requirements must “be commensurate with the specific serious risk[s]” listed in the drug’s labeling, and may “not be unduly burdensome on patient access to the drug, considering in particular . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)[.]” 21 U.S.C. § 355-1(f)(2)(A), (C), (C)(ii). In addition, “to the extent practicable, so as to

minimize the burden on the health care delivery system,” ETASU must “conform with elements to assure safe use for other drugs with similar, serious risks[.]” *Id.* § 355-1(f)(2)(D), (D)(i).

33. A REMS is also subject to periodic review and assessment to ensure the FDA’s balancing of a drug’s risks and benefits reflects the most up to date information. *See* 21 U.S.C. § 355-1(d). A modification or removal of a REMS may be initiated by a “responsible person” (*i.e.*, the drug’s sponsor) or by the Secretary of HHS, who may “require a responsible person to submit a proposed modification to the strategy.” *Id.* § 355-1(g)(4)(A), (B). In addition, the HHS Secretary must “periodically evaluate” the ETASU “to assess whether the elements (i) assure safe use of the drug; (ii) are not unduly burdensome on patient access to the drug; and (iii) to the extent practicable, minimize the burden on the health care delivery system[.]” *id.* § 355-1(f)(5)(B), and based on this evaluation, the FDA must modify ETASU as appropriate, *id.* § 355-1(f)(5)(C).

4. The FDA Ensures Safe Use of Mifepristone Labeling and REMS Process

a) The Current Mifepristone Regimen

34. Mifepristone, as approved by the FDA, is safe. Between 2000 and 2018, over 3.7 million women in the United States used mifepristone to end an early pregnancy. According to the FDA, this medication “has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare.”⁹ The FDA observed in March 2016 that serious adverse events following mifepristone use are “exceedingly rare” and “the numbers of these adverse events appear to be

⁹ U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., *Application Number: 020687Orig1s020: Medical Review(s)* 12 (Mar. 29, 2016) [hereinafter *2016 Medical Review*] (citation omitted) (attached hereto as Exhibit A), also available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf.

stable or decreased over time.”¹⁰ The risks of using mifepristone are estimated to be fourteen times lower than the risks women face by carrying a pregnancy to term.

35. The FDA’s April 11, 2019 approval of GBP’s ANDA reflects the FDA’s determination that GBP’s product, Mifepristone tablets, 200 mg, is therapeutically equivalent to Mifeprex and can be safely substituted for Mifeprex. Like Mifeprex, the approved generic product is indicated for the medical termination of intrauterine pregnancy through 70 days gestation. GBP’s Mifepristone tablets are subject to the same requirements and restrictions as Mifeprex, including the current label and REMS, and can be safely substituted for Mifeprex.¹¹

36. Under the FDA-approved mifepristone/misoprostol regimen, only a certified healthcare provider may prescribe Mifepristone tablets, but the provider need not prescribe the medication in-person.¹² After prescription, on Day One, a patient initiates a medicated abortion by taking one 200 mg tablet of mifepristone in a single oral dose. Then, 24 to 48 hours later, she takes four 200 mcg tablets of misoprostol buccally (*i.e.*, by placing in the area between the cheek and the gums). The FDA label does not specify where a patient should be located when she takes either doses of medication. Most patients will expel the pregnancy within 2 to 24 hours after taking the misoprostol. A patient is instructed to follow up with her health care provider approximately 7 to 14 days later to confirm that the termination of the pregnancy was successful, but the FDA label does not require that this follow-up evaluation occur in-person.

¹⁰ *Id.* at 47.

¹¹ GBP’s Mifepristone tablets are the only generic, FDA-approved medication for pregnancy termination.

¹² Although not yet formalized in the REMS for mifepristone, in April 2021, the FDA announced that it would no longer enforce the requirement that mifepristone be dispensed in-person. In December 2021, the FDA confirmed that the forthcoming revised mifepristone REMS will formally eliminate the in-person requirement. See U.S. FOOD & DRUG ADMIN., *Questions and Answers on Mifeprex* (Dec. 16, 2021) [hereinafter *Questions and Answers on Mifeprex*], <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifeprex>.

37. Under the current REMS (which applies to both the brand name Mifeprex and Plaintiff GBP's generic Mifepristone tablets):

- a. Mifepristone must be ordered, prescribed and dispensed by or under the supervision of a healthcare provider who prescribes and who meets certain qualifications;¹³
- b. Healthcare providers who wish to prescribe Mifepristone must complete a Prescriber Agreement Form attesting to their qualifications prior to ordering and dispensing Mifepristone;
- c. Mifepristone may only be dispensed in clinics, medical offices, and hospitals by or under the supervision of a certified healthcare provider;¹⁴
- d. The healthcare provider must obtain a signed Patient Agreement Form before dispensing Mifepristone, give the patient a copy, and keep a copy of the signed agreement in the patient's chart;
- e. Healthcare providers who prescribe Mifepristone are required under FDA regulations to provide the patient with a copy of the Mifepristone Medication Guide (FDA-approved information for patients).¹⁵

38. In essence, the existing REMS requirements for mifepristone fall into three general categories: (1) prescribers: the restrictions that only certified healthcare providers may prescribe the medication; (2) safe use: restrictions on how the medication should be dispensed and administered to patients and the conditions required to address safety issues; and (3) informed consent: what information patients should receive about the risks of taking the medication. The mifepristone REMS program also imposes certain requirements for tracking distribution of the

¹³ In connection with removing the in-person dispensing requirement, the FDA announced that the forthcoming revised REMS will only require that mifepristone be "prescribed by or under the supervision of a certified healthcare provider who meets certain qualifications." See *supra* note 1, *Mifeprex (mifepristone) Information*.

¹⁴ Though the current REMS specify that mifepristone may only be dispensed in certain healthcare settings, in accordance with its April 2021 Notice of Enforcement Discretion (discussed *infra* Section IV(B)(4)(d)), the FDA now allows mifepristone to be dispensed directly by pharmacies and through the mail. See *supra* note 1, *Mifeprex (mifepristone) Information*.

¹⁵ U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., *NDA 020687 Mifeprex (mifepristone) Tablets, 200 mg, Antiprogestational Synthetic Steroid: Risk Evaluation and Mitigation Strategy (REMS)* (Mar. 29, 2016) (attached hereto as Exhibit B), also available at https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf.

medication, confidentiality provisions for prescribers and patients, and recording and reporting adverse events, if any. The FDA has determined that these REMS requirements sufficiently mitigate the risks of mifepristone so as to ensure the medication's benefits outweigh its risks.

b) *Procedural History of Mifepristone REMS*

39. In September 2000, when the FDA granted final marketing approval for mifepristone, in combination with misoprostol, for the termination of pregnancy up to 49 days, the FDA approved the medication under Subpart H (which provides for accelerated approval), and imposed ETASU—a restricted distribution system—as a condition of approval.

40. Pursuant to the 2007 FDA Amendments Act establishing the REMS program, in March 2008 the FDA deemed mifepristone as having a REMS in effect because it already had ETASU in place under Subpart H, and mifepristone continued to be distributed subject to the same restrictions under which it was originally approved.

41. After subsequent review, the FDA issued a new REMS for mifepristone in 2011, which incorporated the same restrictions in place when the medication was initially approved: (i) a Medication Guide to be dispensed with each prescription; (ii) three types of ETASU (A, C, D – discussed below); (iii) an implementation system governing where the medication may be shipped and requirements for maintaining confidential records tracking shipments, proof of delivery, etc.; and (iv) requiring the sponsor to submit a REMS assessment to the FDA one year following initial approval and every three years thereafter.

42. The specific ETASU imposed for mifepristone under the 2008 and 2011 modifications to the mifepristone REMS program provided detailed requirements governing who may prescribe and purchase the medication.

43. ETASU A restricted those who may prescribe mifepristone to Certified Prescribers who executed a Prescriber's Agreement agreeing to meet certain qualifications and to follow the

guidelines outlined therein. Under the 2008 and 2011 REMS, certified prescribers were required to be physicians with the ability to date a pregnancy and diagnose an ectopic pregnancy; who had made plans for a patient to receive follow-up abortion care in cases of incomplete abortion or severe bleeding, and ensured a patient's access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and had read and understood the prescribing information for the medication. In addition, the prescriber agreed to provide the patient with the Medication Guide and Patient Agreement, gave the patient an opportunity to read and discuss them, obtained her signature, and then signed it himself or herself; notified the manufacturer of any cases of incomplete abortion, hospitalization, transfusion, or other serious event; and recorded the unique serial number on each package of Mifeprex in each patient's record.

44. ETASU C restricted where a patient may receive mifepristone. The medication could only be dispensed in certain health care settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a prescriber certified under ETASU A; it could not be dispensed through retail pharmacies or sold over the internet.

45. ETASU D ensures that patients prescribed mifepristone receive, and certify that they have received, specific safety information about the medication. Mifepristone may only be dispensed to a patient who has completed and signed a Patient Agreement form, a copy of which must be placed in her medical record, and been provided a copy of the FDA-required Medication Guide.

c) *The 2016 Mifepristone Labeling and REMS Revisions*

46. Initiated in 2015 and completed in 2016, the FDA conducted a lengthy review of the mifepristone label and REMS. As part of that review, the FDA assembled a number of internal teams to evaluate safety monitoring data collected through the REMS program and additional medical and clinical research on mifepristone.

47. As a result of this review and based on the growing body of evidence about the safety of mifepristone, the FDA revised the label to reduce the recommended dosage from three 200 mg tablets to one 200 mg tablet and removed the requirement that a patient's follow-up assessment within 7 to 14 days after taking the medication be an in-person examination.

48. The FDA also approved two changes regarding *where* the patient ingests the mifepristone and misoprostol. First, the label no longer requires that a patient take the mifepristone and misoprostol "at [her] provider's office," or under direct observation by a health care provider.¹⁶ The label advises the healthcare provider to "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."¹⁷ The change in this requirement was significant: it allowed a patient to self-administer both medications in the location of her choosing and reflected the FDA's determination that direct observation of medication ingestion by a medical professional was not necessary to ensure patient safety.

49. Second, the new label clarified that mifepristone is safe for use through 70 days of pregnancy (rather than the previous 49).¹⁸ The FDA's 2016 Medical Review concluded that, based on the available scientific evidence, "[m]edical termination of pregnancies through 70 days gestation is safe and effective and should be approved."¹⁹

50. As part of its 2016 labeling revision, the FDA also undertook to "assess[] the current REMS program to determine whether each Mifeprex REMS element remains necessary to

¹⁶ *Mifeprex Medication Guide* (Mar. 2016) (attached hereto as Exhibit C), also available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

¹⁷ *Id.* at 3.

¹⁸ *Id.* at 2.

¹⁹ See *supra* note 9, Ex. A (2016 Medical Review) at 21.

ensure that the drug’s benefits outweigh the risks.”²⁰ This assessment was conducted by a multidisciplinary reviewing team and reviewed by the Commissioner of the FDA, who gave specific feedback on proposed changes to the Mifepristone REMS.²¹

51. The FDA’s justifications for the 2016 label changes, including the REMS revisions, were documented in detail in at least several internal memoranda.²² In evaluating each element of the REMS, the FDA considered “safety data gathered over the past 16 years since approval, and information about current clinical practice.”²³

52. Following this review, the FDA “continue[d] to believe that a REMS is necessary to ensure the benefits [of Mifeprex] outweigh the risks” and reauthorized the REMS program, including all of the ETASU, with several modifications.²⁴ Significantly, the 2016 REMS removed the previous requirement that a certified prescriber of mifepristone be a physician, allowing other types of healthcare providers with prescriptive authority²⁵ to prescribe mifepristone, provided they

²⁰ U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., *Application Number: 020687Orig1s020, Supplement Approval Letter 2* (Mar. 29, 2016) (attached hereto as Exhibit D), also available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020Approv.pdf.

²¹ U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., *Application Number: 020687Orig1s020, Cross Discipline Team Leader Review* (Mar. 29, 2016) [hereinafter *Cross Discipline Team Leader Review*] (attached hereto as Exhibit E), also available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf.

²² See *supra* note 9, Ex. A (*2016 Medical Review*); *supra* note 21, Ex. E (*Cross Discipline Team Leader Review*); U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., *Application Number: 020687Orig1s020, Summary Review* (Mar. 29, 2016) (attached hereto as Exhibit F), also available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020SumR.pdf; U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., *Application Number: 020687Orig1s020, Risk Assessment and Risk Mitigation Review(s)* (Mar. 29, 2016) [hereinafter *2016 REMS Modification*] (attached hereto as Exhibit G), also available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RiskR.pdf.

²³ *Supra* note 22, Ex. G (*2016 REMS Modification*) at 30 (citations omitted).

²⁴ *Id.* at 5 (explaining rationale for proposed REMS modifications), 8 (listing changes and discussing retention of ETASU D), 12–17 (detailing addendum to REMS modification review).

²⁵ Which healthcare providers have prescriptive authority varies state-by-state, and may include nurse practitioners, physicians’ assistants, nurse midwives, advanced practice registered nurses, and other master’s degree-level health care providers, depending on state law.

abide by the remaining certified prescriber requirements in the REMS (which include the ability to accurately date a pregnancy and other relevant qualifications).²⁶

d) *The 2021 REMS Revisions*

53. As a result of the COVID-19 pandemic and in response to a request from medical professionals, in April 2021, the FDA halted enforcement of the in-person dispensing requirement for mifepristone, thus allowing mifepristone to be prescribed remotely (often referred to as “telemedicine”), and to be dispensed directly by a pharmacy or by mail.²⁷ The FDA explained that, based on its review of reported adverse events and studies pertinent to the in-person dispensing requirement, elimination of the in-person dispensing requirement would not result in increased serious safety concerns.²⁸

54. Following that decision, the FDA again conducted a thorough review of the mifepristone REMS, as it had in 2016. The FDA found that certain modifications were necessary “to reduce burden on patient access and the health care delivery system and to ensure the benefits of the product outweigh the risks.”²⁹

55. Though the changes to the REMS have not yet been finalized, the FDA has confirmed that the revised REMS will formally eliminate the in-person dispensing requirement.³⁰ In the meantime, the FDA continues to allow remote prescribing and dispensing in accordance

²⁶ *Supra* note 21, Ex. E (*Cross Discipline Team Leader Review*).

²⁷ See U.S. FOOD & DRUG ADMIN., Letter from Janet Woodcock, M.D. to Maureen Phipps, M.D., M.P.H., F.A.C.O.G. and William Grobam, M.D., M.B.A. (Apr. 12, 2021), https://www.aclu.org/sites/default/files/field_document/fda_acting_commissioner_letter_to_acog_april_12_2021.pdf.

²⁸ *Id.*

²⁹ *Supra* note 12, *Questions and Answers on Mifeprex*.

³⁰ *Id.*

with the April 2021 Notice of Enforcement Discretion. The 2021 REMS will also add a requirement that pharmacies be certified to dispense mifepristone.

C. Mississippi Laws Regulating Mifepristone Conflict with the REMS

56. The Mississippi Legislature has passed, and the Mississippi Department of Health enforces, a number of laws and regulations that restrict the administration of mifepristone, in direct conflict with FDA's approval of and regimen for mifepristone.

a) *The Mississippi Abortion Ban*

57. On July 7, 2022, a near-total ban on abortion, including medicated abortion, went into effect in Mississippi. *See* MISS. CODE ANN. § 41-41-45. Accordingly, Mississippi now prohibits all abortions, "except in the case where necessary for the preservation of the mother's life or where the pregnancy was caused by rape." *Id.* 41-41-45(2). The law defines abortion as "the use or prescription of any instrument, *medicine, drug* or any other substance or device to terminate the pregnancy of a woman known to be pregnant with an intention other than to increase the probability of a live birth, to preserve the life or health of the child after live birth or to remove a dead fetus." *Id.* 41-41-45(1) (emphasis added).

58. The ban specifies that

[a]ny person, except the pregnant woman, who purposefully, knowingly or recklessly performs or attempts to perform or induce an abortion in the State of Mississippi, except in the case where necessary for the preservation of the mother's life or where the pregnancy was caused by rape, upon conviction, shall be punished by imprisonment in the custody of the Department of Corrections for not less than one (1) year nor more than ten (10) years.

MISS. CODE ANN. § 41-41-45(4).

59. Under Mississippi law, except in rare circumstances, it is now illegal for providers to prescribe mifepristone for its FDA-approved use to terminate a pregnancy. The day the ban

went into effect, the only abortion clinic in Mississippi that provided abortions—surgical or medicated—was forced to close.³¹

60. Additionally, Mississippi law specifies that any “person who sells . . . or offers to sell . . . any drug or medicine, for causing unlawful abortion . . . or who manufactures any such article or medicine, is guilty of a misdemeanor, and, on conviction, shall be punished by fine . . . and by imprisonment.” MISS. CODE ANN. § 97-3-5. The State has thus not only criminalized performing or attempting to perform a medicated abortion, but selling or manufacturing any abortion-inducing medication for use in connection with an unlawful abortion.

61. The Mississippi abortion ban directly conflicts with the FDA’s statutorily-authorized REMS for mifepristone, as it prevents access to an FDA-approved medication that has been deemed safe and effective. Congress granted the FDA the authority to issue a REMS to ensure that the benefits of a medication outweigh its risks. By eliminating access to mifepristone, Mississippi is preventing its citizens from benefiting from mifepristone’s intended use.

62. The FDA’s comprehensive approval process for prescription drugs and, specifically, mifepristone, ensures appropriate protocols for their safe and effective use. Mississippi law now prevents almost all use of mifepristone, flouting the FDA’s approval and authorized regimen.

b) *Mississippi Regulations that Restrict Access to Mifepristone*

63. In the limited circumstances in which a Mississippi woman may obtain an abortion—when her life is at stake or she has filed a formal rape charge—Mississippi imposes onerous requirements that further limit access to mifepristone. For example, in 2013, Mississippi

³¹ A. Martinez & Diane Derzis, *Mississippi’s Only Abortion Clinic Has Closed its Doors for Good: 7-Minute Listen*, NPR (July 7, 2022, 7:20 AM ET), <https://www.npr.org/transcripts/1110222245>.

implemented The Women’s Health Defense Act of 2013, S.B. 2795, 2013 Reg. Sess. (Miss. 2013) (codified as amended at MISS. CODE ANN. §§ 41-41-101–117) (“the 2013 Act”). The 2013 Act is aimed squarely at regulating the provision of abortion-inducing drugs in Mississippi and purports to “[p]rotect women from the dangerous and potentially deadly use of abortion-inducing drugs when administration of the drugs does not meet the standard of care; and [e]nsure that physicians meet the standard of care when giving, selling, dispensing, administering or otherwise providing or prescribing abortion-inducing drugs.” *Id.* § 41-41-103(2). In so doing, the 2013 Act places strict limitations on who may prescribe and administer mifepristone and the circumstances in which they may do so. These limitations, like the abortion ban, conflict with the FDA’s determination of the necessary and sufficient conditions for mifepristone’s safe use.

64. The 2013 Act squarely conflicts with the FDA’s REMS conditions for mifepristone on all three broad categories of restrictions: prescribers, safe use, and informed consent. For example, the 2013 Act mandates that only a physician licensed in Mississippi may “give, sell, dispense, administer or otherwise provide or prescribe any abortion-inducing drug.” MISS. CODE ANN. § 41-41-107(1) (the “physician only” provision). But the state-imposed restrictions go even further: Mississippi law requires additional training before a physician may prescribe abortion-inducing medication, such that not only is administration of mifepristone restricted to physicians only (already in direct conflict with the FDA-mandated standard), but not even every licensed physician in Mississippi may prescribe the medication, only those who have completed at least one year of postgraduate training in a training facility with an approved residency program and an additional year of obstetrics/gynecology residency. 15 MISS. CODE R. §§16-1-44.1.1, 16-1-44.1.4 (24).

65. In addition to the severe prescriber restrictions, the 2013 Act requires a series of in-person interactions between physician and patient, effectively banning telemedicine and the remote provision of healthcare, which the FDA now allows for mifepristone. Thus, even though Mississippi now permanently allows telemedicine for other healthcare needs, MISS. CODE ANN. § 83-9-351, and the state has recognized that telemedicine reduces barriers to healthcare,³² remote healthcare is unavailable for medicated abortions. In Mississippi, physicians are required to physically examine a patient prior to “giving, selling, dispensing, administering or otherwise providing or prescribing the abortion-inducing drug.” MISS. CODE ANN. § 41-41-107(2). Once the medication is prescribed, a patient must ingest the medication “in the same room and in the physical presence of the physician who gave, sold, dispensed or otherwise provided or prescribed the drug or chemical to the patient.” *Id.* § 41-41-107(3). Physicians must report the provision of any abortion-inducing medications for the purpose of inducing an abortion to the Mississippi Department of Health. *Id.* § 41-41-109.

66. Mississippi’s in-person requirements continue even after a patient ingests mifepristone. The 2013 Act further requires the prescribing physician to schedule a follow-up visit with a patient approximately 14 days after administration of an abortion-inducing drug. MISS. CODE ANN. § 41-41-107(5), (6). Any physician who is unable to provide follow-up care must have a signed contract with an alternative physician who is available to provide a patient with the mandated in-person care. *Id.*

³² See Kobbie Vance, *Mississippians Now Have Permanent Access to Telehealth*, MPB NEWS (modified May 17, 2022), <https://www.mpbonline.org/blogs/news/mississippians-now-have-permanent-access-to-telehealth/>. In fact, Mississippi State Department of Health Epidemiologist, Dr. Paul Byers, stated that allowing telemedicine is a “big win” for the state, “[p]articularly for Mississippi, when we look at where providers are, and health disparities, and even disparities of where there may be a county where the nearest provider is 50 miles away. And that by itself creates a barrier for that person to access routine care. I think that’s a huge win.” *Id.*

67. As Mississippi does not carve out unique provisions for medicated abortion, provision of mifepristone is subject not only to the 2013 Act governing abortion-inducing drugs, but to the full compendium of the state's abortion regulations. This has a significant impact on both where a patient may be administered the mifepristone and the information a prescriber is required to present to a patient before he or she may prescribe mifepristone.

68. In addition to mandating that the drug must be ingested in the presence of a physician, Mississippi imposes severe restrictions on the physical facilities in which the drug's administration must occur. Under Mississippi law, all Mississippi facilities providing abortion care, which by definition includes administering abortion-causing drugs (mifepristone), MISS. CODE ANN. § 41-75-1(e), must be licensed as either a Level I or Level II Abortion Facility (though the distinction between the two is unclear, as Mississippi regulations require that a Level I abortion facility "meet minimum standards for Level II abortion facilities and Minimum Standards of Operation For Ambulatory Surgical Facilities as established by the licensing agency." 15 MISS. CODE R. § 16-1-44.1.5(9)). An abortion facility is defined as any healthcare facility that conducts 10 or more abortions per calendar month in any calendar year; or, if the facility is open less than 20 calendar days per month, if the facility conducts the pro-rated equivalent of 10 abortions per month if the facility were open so many days per month; or if the facility conducts 100 abortions in any calendar year regardless of the number of abortions per month. *Id.* § 16-1-44.1.5(3). Any facility wishing to administer mifepristone with any regularity is thus subject to all corresponding abortion facility licensing regulations, including the "Minimum Standards of Operation for Abortion Facilities." MISS. CODE ANN. § 41-75-1(e), (h). Per Mississippi regulations, 15 MISS. CODE R. § 16-1-44.28.1, the Minimum Standards of Operation for Abortion Facilities require each such facility to have:

1. Examination Room(s). Rooms for examination shall have a minimum floor area of 80 square feet, excluding vestibules, toilets, and closets. Room arrangement should permit at least 2 feet 8 inches clearance at each side and at the foot of the examination table. A hand-washing fixture shall be provided.
2. Procedure Room. Procedure rooms shall have a minimum floor area of 120 square feet, excluding vestibule, toilet, and closets. The minimum room dimension shall be 10 feet. A scrub sink with knee, elbow, wrist, or foot control, soap dispenser, and single service towel dispenser will be available. All finishes shall be capable of repeated cleaning.
3. Recovery Room. One or more recovery rooms containing sufficient beds for recovering patient shall be provided. Reclining type vinyl upholstered chairs may be substituted in lieu of beds. Direct visual observation of the patients shall be possible from a central vantage point, yet patients shall have a reasonable amount of privacy.

69. In addition, abortion facilities must also meet the minimum standards of operation for ambulatory surgical centers, as established by the Mississippi Department of Public Health. 15 MISS. CODE R. § 16-1-44.1.5(9). Among voluminous requirements, ambulatory surgical centers are required to be “located in an attractive setting” and within 15 minutes travel time from a hospital which has an emergency room. *Id.* § 16-1-42.30.1. Ambulatory surgical centers have stringent construction requirements, including, for example, that all corridors used by patients be at least six feet wide and all patient rooms have, at minimum eight foot ceilings. *Id.* §§ 16-1-42.27, 16-1-42.30.

70. In addition to the extensive facility regulations, abortion facilities are required to have agreements for transportation and care in the case of patient emergency. MISS. CODE ANN. §§ 41-75-1, 41-75-29.

71. In addition to the conflicting prescriber and safe use restrictions described above, Mississippi also imposes an alternate scheme related to the information a patient must receive (about the risks of the drug, specifically, and abortion, generally), before she can receive

mifepristone. These requirements include an initial, in-person meeting with a physician to discuss the risks of the abortion procedure and present a patient with alternative options to abortion, a mandatory fetal ultrasound imaging and auscultation of fetal heartbeat, and a 24-hour waiting period before a patient may proceed with an abortion. MISS. CODE ANN. §§ 41-41-33, 41-41-34.

72. Mississippi also requires, prior to an abortion procedure (including medication-induced abortion), that a physician offer a woman additional information and counseling, including a list of adoption agencies and “[m]aterials designed to inform the woman of the probable anatomical and physiological characteristics of the unborn child at two-week gestational increments from the time when a woman can be known to be pregnant to full term,” which must include “color pictures representing the development of the child at two-week gestational increments” that “contain the dimensions of the unborn child and must be realistic.” MISS. CODE ANN. § 41-41-35(1)(b).

73. These state laws and regulations conflict with the FDA’s scheme for the safe and effective use of mifepristone, and are an obstacle to fulfilling the full purpose and objectives of Congress’s grant of authority to a federal agency to balance the risks and benefits of and design risk mitigation strategies for the administration of prescription drugs in the United States.

D. The Impact of Mississippi’s Unconstitutional Restrictions on Mifepristone

74. Defendant’s actions in enforcing the state of Mississippi’s laws and regulations that conflict with the FDA’s requirements for the safe use of mifepristone frustrate the FDA’s purpose in regulating mifepristone, upsetting the balance that the FDA has struck to protect the public safety, and causing real and direct harm to GBP by foreclosing GBP from selling mifepristone in Mississippi.

75. Mississippi has made it essentially impossible for GBP to sell mifepristone in Mississippi. Although the abortion ban does not do so by name, it functions as a de facto ban on

mifepristone. The ban not only prohibits the use of mifepristone for its FDA-intended purpose in all but the narrowest of circumstances but, as a result of the ban, the only abortion clinic that provided medicated abortions in Mississippi closed on July 7, 2022. The de facto ban and restrictions on mifepristone render it illegal and, in the limited circumstances when it is not illegal, futile for GBP to even attempt to sell its product, as the ban and restrictions plainly prevent and deter providers from prescribing mifepristone.

76. GBP invested substantial money and effort in the research and development of its generic mifepristone and worked closely with the FDA to gain approval for its product. GBP is currently the only licensed ANDA holder approved to market and sell generic mifepristone in the United States.

77. GBP has sold and shipped its mifepristone tablets to providers in 47 states and the District of Columbia. Since GBP received FDA-approval in April 2019 to market and sell mifepristone, GBP has captured a significant share of the nationwide market for mifepristone.

78. Before the Mississippi abortion ban went into effect, there was only one clinic in Mississippi that performed abortions, surgical or medicated. GBP did not sell mifepristone to the former Jackson-based clinic because the Jackson clinic had a Prescriber Agreement in place with Danco, which was entered into before GBP received FDA-approval to sell its generic version of mifepristone.

79. However, GBP had—and continues to have—a Prescriber Agreement in place with Planned Parenthood Southeast, Inc., which has clinics in Georgia, Alabama, and Hattiesburg, Mississippi. GBP has provided mifepristone to the Planned Parenthood Southeast clinics that perform medicated abortions. On information and belief, the Hattiesburg clinic was previously—and remains—unable to provide abortions, surgical or medicated, due to Mississippi's restrictions

on medicated abortion. On information and belief, but for Mississippi's regulations restricting who could prescribe mifepristone and under what conditions, the Hattiesburg clinic would have provided medicated abortions and would have purchased GBP's mifepristone tablets to do so under the Prescriber Agreement already in place.

80. Since the Mississippi abortion ban went into effect, the Jackson clinic has closed. Though the Hattiesburg clinic remains open, like before, it does not provide any abortion services because of the Mississippi restrictions and now ban. Thus, there are no abortion clinics to which GBP may sell its product, notwithstanding demand for mifepristone.

81. Barriers to access often lead to increased use of illicit markets (including online sales), for medications in the United States, and mifepristone is no exception. A recently published peer-reviewed study shows that states with the most restrictive access to abortion in a clinic setting have the highest rates of online requests for the medication—Mississippi is at the top of that list.³³

82. The FDA has determined how mifepristone should be prescribed to women in the United States through the REMS.³⁴ Although the FDA now allows certified providers to prescribe mifepristone remotely, the FDA is clear that mifepristone requires a prescription for use. The REMS thus prohibits purchasing mifepristone directly from online sources without a valid prescription. In fact, the FDA has placed a red, highly visible warning—"Do Not Buy Mifeprex or its Approved Generic Over the Internet"—on its mifepristone information page, referring

³³ Abigail Aiken et al., *Demand for Self-Managed Medication Abortion Through an Online Telemedicine Service in the United States*, 110 AM. J. PUB. HEALTH 90 (2020), <https://ajph.aphapublications.org/doi/pdfplus/10.2105/AJPH.2019.305369>; see also Abigail Aiken et al., *Motivations and Experiences of People Seeking Medication Abortion Online in the United States*, 50 PERSP. SEXUAL REPROD. HEALTH 157 (2018), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8256438/pdf/nihms-1715998.pdf>.

³⁴ *Supra* note 1, *Mifeprex (mifepristone) Information*.

visitors to the FDA’s consumer safety guide to buying prescription medicines online,³⁵ and has been cracking down on websites that attempt to bypass the FDA’s safeguards for prescribing and distributing mifepristone. In 2019, the FDA issued a warning letter to an online pharmacy selling misbranded and unapproved medicated abortion drugs to women in the United States outside the protections of the FDA-approved REMS program.³⁶

83. Notwithstanding that mifepristone is not supposed to be sold over the internet without a valid prescription, some women are in fact buying it online—including women in Mississippi, who will likely turn to the internet for mifepristone in larger droves in the wake of the abortion ban.³⁷ Thus, Mississippi’s unconstitutional restrictions are pushing women to buy mifepristone (or what purports to be mifepristone) outside the scope of the FDA’s approval and in violation of the FDA’s thoroughly evaluated and balanced risk mitigation plan, potentially increasing the risks to those women—the exact opposite of what the FDA is trying to accomplish with the REMS.³⁸

³⁵ *Id.*

³⁶ U.S. FOOD & DRUG ADMIN., *Warning Letter from FDA to Aidaccess.org: MARCS-CMS 575658, Re: Causing the Introduction of a Misbranded and Unapproved New Drug into Interstate Commerce – March 08, 2019* (Mar. 12, 2019), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019>; U.S. FOOD & DRUG ADMIN., *Warning Letter from FDA to Rablon: MARCS-CMS 1111111, Re: Causing the Introduction of a Misbranded and Unapproved New Drug into Interstate Commerce – March 08, 2019* (Mar. 12, 2019), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/rablon-1111111-03082019>.

³⁷ A recent study found that demand for online abortion medication increased in Texas after Texas enacted a law banning abortions after six weeks. Abigail Aiken et al., *Association of Texas Senate Bill 8 With Requests for Self-managed Medication Abortion*, 5 JAMA NETWORK OPEN 2 (2022), <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789428>.

³⁸ In fact, Aid Access, an online-only, European-based organization that previously received a warning letter from the FDA to discontinue selling unapproved abortion drugs reported that, since *Roe v. Wade*, 410 U.S. 113 (1973) was overturned by *Dobbs v. Jackson Women’s Health Organization*, No. 19-1392, 579 U.S. ____ (2022), the organization has been receiving 4,000 requests a day for abortion medication, up from previous averages of 600-700 requests a day. See David Ingram, *A Dutch Doctor and the Internet are Making Sure Americans Have Access to Abortion Pills*, NBC NEWS (July 7, 2022, 6:00 AM PDT),

84. GBP is effectively precluded from selling its product in Mississippi. Imposition of unconstitutional state law restrictions on the prescription and use of mifepristone causes, and will continue to cause, significant revenue loss to GBP.

85. In addition, Defendant's conduct, unless enjoined, will cause immediate and irreversible harm to the reputation and goodwill of mifepristone and GBP. The State of Mississippi's effective ban and unnecessary regulation of mifepristone are likely to cause physicians and patients—both in Mississippi and across the country—wrongly to believe that mifepristone is not a safe and effective medication, thus adversely affecting GBP's primary product on the market.

COUNT I

(United States Constitution: Preemption)

86. GBP realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 85 of the Amended Complaint as though set forth fully herein.

87. The Supremacy Clause of the United States Constitution provides that federal laws made under the authority of the United States shall be the "supreme law of the land," the laws of any state to the contrary notwithstanding. U.S. CONST. art. VI, cl. 2.

88. The Supremacy Clause mandates that federal law preempts any state regulation that poses an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.

<https://www.nbcnews.com/tech/tech-news/dutch-doctor-internet-are-making-sure-americans-access-abortion-pills-rcna35630>.

89. Under the FDCA, Congress has delegated to the FDA the authority to protect and promote the public health by approving for public use “safe and effective” prescription drugs.

90. Prescription drug regulation is an arena that is inherently national in nature in that the FDA has long set uniform standards for drug regulation across all states. In 2016, the FDA reviewed and amended the labeling and REMS requirements for mifepristone and concluded that the amended restrictions were set at the appropriate level to best balance the risks and benefits of mifepristone. In 2021, the FDA determined it was necessary to modify the REMS to reduce the burden on patient access to mifepristone. Those decisions were grounded in careful review of the underlying science, consistent with regulatory and statutory requirements, and fall squarely within the federal agency’s realm of expertise and authority as delegated by Congress.

91. Mississippi imposes its own state laws and regulations that conflict with the FDA’s approved regimen and risk mitigation strategies for mifepristone.

92. Mississippi’s conflicting state laws are an obstacle to the accomplishment and execution of the full purposes and objectives of Congress in granting the authority to the FDA to both approve and determine the appropriate measures to mitigate the risks of prescription drugs in the United States.

93. Taken as a whole, Mississippi’s conflicting state laws represent an impermissible effort by Mississippi to establish its own drug approval policy and directly regulate the availability of FDA-approved drugs within the state. Mississippi’s laws conflict with the FDA’s mandate under the FDCA, disregard federal policies, undermine the FDA’s comprehensive regulatory scheme for nationally-effective drug approvals, and otherwise impede the accomplishment and execution of the full purposes and objectives of federal law.

94. Mississippi's conflicting state laws also specifically undermine the FDA's assessment that mifepristone is a safe and effective product that may be distributed and safely administered in all fifty states and to which patients should have access. In so doing, it impedes the FDA's congressional mandate to approve a range of safe treatments to promote the public health.

95. Plaintiff has no adequate remedy at law for these violations of the Supremacy Clause.

96. Mississippi's conflicting state laws cause, and will continue to cause, substantial injury to GBP unless the state restrictions are vacated and Defendant is enjoined from imposing or enforcing these restrictions.

COUNT II

(United States Constitution: Commerce Clause)

97. GBP realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 96 of the Amended Complaint, as though set forth fully herein.

98. The Commerce Clause of the United States Constitution, U.S. CONST. art. I, § 8, cl. 3, prevents a state from taking any action that may fairly be deemed to have the effect of impeding the free flow of trade between the states.³⁹

99. Mississippi's restrictions on mifepristone impose significant burdens on interstate commerce because they interfere with the FDA's national and uniform system of regulation. Mississippi (and other states) cannot be allowed to make its own determinations as to how the risks and benefits of prescription drugs should be weighed and whether and how prescription drugs

³⁹ See *Freeman v. Hewit*, 329 U.S. 249, 252 (1946).

should be approved, regulated, administered, and available within the state. If it is, the result will be an unworkable patchwork of state-specific regulation governing whether prescription drugs are available and how prescription drugs are administered, which would effectively eviscerate the mission of the FDA and create different (and potentially conflicting) sets of rules for deciding who can access which medications and what constitutes safe and effective pharmaceuticals.

100. Mississippi's conflicting regulations also impose significant burdens on interstate commerce because they harm patients living in Mississippi, as well as patients residing outside of Mississippi who see health care providers in the state. Because health care providers are restricted in their ability to prescribe mifepristone to patients (regardless of their state of residence), patients across several states are unable to access mifepristone thus impacting commerce beyond the borders of the state.

101. The burden imposed on interstate commerce by Mississippi's conflicting regulations is clearly excessive in relation to the purported protections touted by the state legislature. The additional restrictions on provision and use of mifepristone in Mississippi above and beyond those imposed by the FDA are excessive, especially in light of the FDA's careful and comprehensive balancing of the risks and benefits of such medication for the public health as evidenced, generally, by its approval of the drug and by the REMS process, in particular.

102. GBP has no adequate remedy at law for the violation of the Commerce Clause.

103. Mississippi's conflicting regulations will cause substantial injury to GBP unless the state restrictions are vacated and Defendant is enjoined from imposing these restrictions.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully prays for the following relief:

- A. A declaration pursuant to 28 U.S.C. § 2201 that the state of Mississippi's laws and regulations restricting provision and use of FDA-approved abortion-inducing drugs violate the United States Constitution;
- B. Permanent injunctive relief and/or a final order enjoining the Defendant from enforcing any state law or regulation banning medicated abortion or restricting the provision and use of mifepristone beyond those outlined by the FDA's REMS for mifepristone. In the alternative, permanent injunctive relief and/or a final order vacating any state law or regulation restricting the provision and use of mifepristone beyond those outlined by the FDA's REMS for mifepristone;
- C. An order awarding plaintiff's costs, expenses and attorneys' fees; and/or
- D. Such other and further relief as the Court deems just and appropriate.

Dated: July 21, 2022

Respectfully submitted,

GENBIOPRO, INC.

By Its Attorneys,

BAKER DONELSON BEARMAN
CALDWELL & BERKOWITZ, PC

By: s/ J. Carter Thompson, Jr.

J. CARTER THOMPSON, JR.

OF COUNSEL:

J. Carter Thompson, Jr. (MSB No. 8195)

cthompson@bakerdonelson.com

D. Sterling Kidd (MSB #103670)

skidd@bakerdonelson.com

BAKER DONELSON BEARMAN CALDWELL & BERKOWITZ, PC

One Eastover Center

100 Vision Drive, Suite 400 (ZIP 39211)

Post Office Box 14167

Jackson, MS 39236-4167

Telephone: (601) 351-2400

Facsimile: (601) 351-2424

U. Gwyn Williams (admitted *pro hac vice*)

Gwyn.williams@lw.com

Kenneth J. Parsigian (admitted *pro hac vice*)

kenneth.parsigian@lw.com

Avery E. Borreliz (admitted *pro hac vice*)

Avery.borreliz@lw.com

LATHAM & WATKINS LLP

200 Clarendon Street, 27th Floor

Boston, MA 02116

Telephone: (617) 880-4500

EXHIBIT A

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s020

MEDICAL REVIEW(S)

Clinical Review:

(b) (6) and (b) (6)
NDA 020687/S-020- Mifeprex

CLINICAL REVIEW

Application Type	SE-2 Efficacy Supplement
Application Number(s)	NDA 020687/S-020
Priority or Standard	Standard
Submit Date(s)	May 28, 2015
Received Date(s)	May 29, 2015
PDUFA Goal Date	March 29, 2016
Division / Office	(b) (6)
Reviewer Name(s)	(b) (6) and (b) (6)
Review Completion Date	March 29, 2016
Established Name	Mifepristone
(Proposed) Trade Name	Mifeprex
Therapeutic Class	Progestin antagonist
Applicant	Danco Laboratories, LLC
Formulation(s)	Oral Tablet
Dosing Regimen	For pregnancies through 70 days gestation: Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol.
Indication(s)	Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.
Intended Population(s)	Pregnant women who desire a medical termination through 70 days gestation.

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1 Recommendations/Risk Benefit Assessment

This NDA supplement from the Applicant, Danco Laboratories, LLC (called Danco or the Applicant throughout this clinical review), requested the following changes to the NDA for Mifeprex, approved 15 years ago in September 2000.

Changes proposed by the Applicant:

1. Change the dosing regimen: Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally
2. Remove the statement in labeling that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman.
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up needed, but not restricted to in-clinic at 14 days after Mifeprex
5. Increase the gestational age from 49 days to 70 days
6. Change the labeled time for expulsion of the products of conception from 4-24 hours to 2-24 hours post misoprostol administration
7. Add that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change “physician” to “(b) (4)” in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change indication to add reference to use of misoprostol: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation.”
10. Remove references to “under Federal law” from the Prescriber’s Agreement
11. Address the Pediatric Research Equity Act (PREA) requirement for pediatric studies

Each of these 11 items will be discussed in the appropriate section of this review, generally under Section 6: Review of Efficacy and Section 7: Review of Safety. Four of the items, namely Number 8-11, are primarily regulatory and/or legal. They are discussed in Sections 1.3 and 9.4 (REMS recommendations and Prescriber’s Agreement), 7.6.4 (PREA), and 9.2 (Labeling recommendation). Additional information is found in Section 7.7 (2) on the change to “(b) (4)” Section 7.7 (3) on “under Federal law”, and Section 7.7 (4) on the reference to use of misoprostol.

1.1 Recommendation on Regulatory Action

The clinical reviewers recommend an approval action for this efficacy supplement.

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1.2 Risk Benefit Assessment

1. Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally.

The Applicant has submitted sufficient evidence from the published medical literature to demonstrate that decreasing the dose of Mifeprex from 600 mg to 200 mg while increasing the dose of misoprostol from 400 to 800 mcg is safe and efficacious for termination of pregnancy through 70 days gestation. The risk/benefit balance favors approval.

There is sufficient evidence that a dosing regimen with buccal administration of 800 mcg misoprostol is safe and effective. This change in the dosing regimen should be approved.

2. Allow administration of misoprostol outside of the clinic:

Based on the evidence submitted by the Applicant, a dosing regimen that includes administration of misoprostol outside of the clinic is safe and effective for termination of pregnancy through 70 days gestation; labeling should be revised to remove the requirement for in-clinic dosing of misoprostol

3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex:

The available evidence supports that a dosing regimen that provides for administration of misoprostol 24-48 hours after administration of Mifeprex is safe and effective. The risk/benefit assessment demonstrates that this change in the dosing regimen should be approved.

4. Follow-up needed, but not restricted to in-clinic at 14 days after Mifeprex:

Based on the evidence submitted by the Applicant supporting this change, flexibility in timing and method of follow-up after medical abortion is safe. Labeling should be revised to remove the requirement for in-clinic follow-up at 14 days.

5. Increase the gestational age from 49 days to 70 days:

As detailed in the following review, the Applicant has submitted sufficient evidence for the safety and efficacy of medical abortion with Mifeprex, in a regimen with misoprostol, through 70 days gestation. The risk/benefit assessment supports the approval of the new dosing regimen up through 70 days gestation.

6. Change the labeled time for expulsion of the products of conception from 4-24 hours to 2-24 hours post misoprostol administration:

The Applicant has submitted sufficient data from the published medical literature to support approval of a change in the label to note time to expulsion ranges from 2-24 hours.

7. Add that a repeat 800 mcg buccal dose of misoprostol may be used if needed:

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The Applicant has submitted sufficient evidence to support that a repeat dose of misoprostol may be used through 70 days gestation to complete expulsion of the products of conception if needed. The risk/benefit assessment supports approval of this change. There have been rare reports of uterine rupture with use of misoprostol in women with prior uterine scar(s). This information should be added to the Mifeprex label.

8. Change “physician” to “(b) (4)” in the labeling and Risk Evaluation and Mitigation Strategies (REMS) document:

The Applicant has submitted sufficient data to support that Mifeprex is safe and effective when prescribed by midlevel practitioners as well as by physicians. Therefore, the term “licensed physician” was changed in the label and REMS materials to “healthcare provider who prescribes.” This broader category of providers will still have to meet the certification criteria specified in the Prescriber Agreement Form.

9. Change the approved indication to add reference to use of misoprostol: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.” Based on current Agency labeling practice regarding drugs used together in a treatment regimen, the addition of misoprostol to the Indication Statement for Mifeprex should be approved.

10. Remove references to “under Federal law” from the Prescriber Agreement:

The Agency has determined that there is no precedent for using this phrase in other REMS, nor is there any clinical rationale for including it; therefore, it is acceptable to remove “under Federal law” from the Prescriber Agreement Form.

11. Address the Pediatric Research Equity Act (PREA) requirement for pediatric studies:

The Applicant has submitted sufficient evidence from the published medical literature to address the PREA requirement for this supplemental application. The Applicant has demonstrated that Mifeprex is safe and effective in postmenarchal females, including those under 17 years of age. (b) (6) concurred with granting a partial waiver under PREA in patients ages birth to 12 years of age who are premenarche.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Changes proposed in this efficacy supplement entailed a number of modifications to the current Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex. See Section 9.4 for full details. The (b) (6) (b) (6) concurs with the (b) (6) (b) (6) evaluation of the REMS modifications, which include:

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- Removal of “under Federal law” from the Prescriber Agreement Form is acceptable (see discussion in Additional Submissions / Issues).
- The term “healthcare providers who prescribe” is preferable to the Applicant’s proposed “(b) (4)” (see discussion in Additional Submissions / Issues).
- It is appropriate to modify the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber’s Agreement to include “hospitalization, transfusion or other serious event.” Under these requirements, healthcare providers report certain adverse events to the Applicant, which then is required to report the adverse events to FDA. FDA has received such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely. For this reason, ongoing reporting by certified healthcare providers to the Applicant of all of the specified adverse events is no longer warranted. It should be noted that the Applicant will still be required by law, as is every NDA holder, 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.

(b) (6) concurs with the following modifications recommended by (b) (6)

- Removal of the Medication Guide (MG) from the REMS. The MG will remain a required part of labeling and will be required to be provided to patients consistent with the requirements in 21 CFR part 208. FDA has been maintaining MGs as labeling but removing them from REMS when, as here, inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks, such as when the MG is redundant and not providing additional use or information to the patient about the risk(s) the REMS is intended to mitigate. This is consistent with ongoing efforts to streamline REMS by allowing for updates to the MG without need for a REMS modification.
- Removal of the Patient Agreement form (ETASU D). This decision was based on the well-established safety profile of Mifeprex, as well as the fact that the small numbers of practitioners who provide abortion care in the US use informed consent practices that are duplicated of the current Patient Agreement and thus the Patient Agreement is no longer necessary to ensure that the benefits of the drug outweigh the risks.
- Revision of the Prescriber Agreement Form to reflect changes to labeling revisions pursuant to the proposed efficacy supplement, and to improve the flow of the document.
- Revision of the REMS goals to reflect the above changes

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarket requirements or commitments for this efficacy supplement.

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2 Introduction and Regulatory Background

2.1 Product Regulatory Information

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' (7 weeks) pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments." Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets certain qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments that the then-applicant of the Mifeprex NDA (i.e., the Population Council) agreed to meet:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on Day 14 (compliance with return visit) were incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.
2. A surveillance study on outcomes of ongoing pregnancies.

In addition, the 2000 approval letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco).

2.2 Tables of Currently Available Treatments for Proposed Indications

In the US there are no other approved products for the medical termination of first trimester pregnancy. Misoprostol alone or in combination with methotrexate has been used for early medical abortion (MAB), with much lower success than Mifeprex.¹

¹ American College of Obstetricians and Gynecologists. Practice bulletin No. 143: medical management of first-trimester abortion. *Obstet Gynecol* 2014;123(3):676-92. doi:10.1097/01.AOG.0000444454.67279.7d.

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2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues with Consideration to Related Drugs

Korlym (mifepristone) is indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Korlym is taken in oral doses of 300 mg to 1200 mg daily. It is contraindicated in pregnancy, patients taking simvastatin, lovastatin and CYP3A substrates with narrow therapeutic ranges, patients on corticosteroids for lifesaving purposes, and women with unexplained vaginal bleeding or endometrial hyperplasia with atypia or endometrial carcinoma. The label² provides warnings and precautions regarding adrenal insufficiency, hypokalemia, vaginal bleeding and endometrial changes, QT prolongation, exacerbation or deterioration of conditions treated with corticosteroids, use of strong CYP3A inhibitors, and opportunistic infections with *Pneumocystis jiroveci* pneumonia in patients with Cushing's. Adverse reactions noted in $\geq 20\%$ of patients in clinical trials with Korlym included nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite and endometrial hypertrophy.

Reviewer comment:

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

Ella (ulipristal acetate) is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. The **ella** label³ notes that in clinical trials, the most common adverse reactions ($\geq 10\%$) in women receiving **ella** were headache (18% overall) and nausea (12% overall) and abdominal and upper abdominal pain (12% overall).

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

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

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

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days. In clinical trials, cycle length was increased by a mean of 2.5 days but returned to normal in the subsequent cycle. Seven percent of subjects reported menses occurring more than 7 days earlier than expected, and 19% reported a delay of more than 7 days. The label recommends that women rule out pregnancy if the expected menses is delayed by more than one week. Nine percent of women studied reported intermenstrual bleeding after use of ella.

Reviewer comment:

Ella is for occasional use and is not to be used as a regular contraceptive method. As such, the drug is not recommended for repeated use in the same menstrual cycle. The safety and efficacy of repeat use within the same cycle has not been evaluated. A single dose of ella does not appear to result in serious adverse events.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-NDA meeting was held with the Applicant on January 29, 2015. The following items, among others, were discussed:

- New dosing regimen
- Proposal to have (b) (4)
- Use up to (b) (4) days' gestation
- Change in the interval between Mifeprex and misoprostol administration to 24-48 hours
- Revision of the labeled time to expulsion after misoprostol is administered
- Use of the term "(b) (4) in the approval and label to describe who may obtain and dispense Mifeprex
- Deletion of "under Federal law" in the Prescriber's Agreement
- PREA requirements
- Regulatory pathway for approval

2.6 Other Relevant Background Information

Since the approval in France and China in 1988, mifepristone for MAB is currently approved in 62 countries globally⁴; see the list and dates of approval in Appendix 9.7.

Prior to the Mifeprex approval by the FDA, mifepristone had also been approved in the UK in 1991. In the UK, the current therapeutic indications include:

- Medical alternative to surgical termination of intrauterine pregnancy up to 63 days gestation based on the first day of the last menstrual period
- Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination during the first trimester

⁴ Gynuity website, www.gynuity.org, Medical Abortion in Developing Countries- List of Mifepristone Approvals.

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- For use with prostaglandin analogues for termination of pregnancy for medical reasons beyond the first trimester
- Labour induction in foetal death in utero⁵

The estimated cumulative use of Mifeprex in the US since the 2000 approval is 2.5 million uses. Estimated global occurrence of MAB and SAB combined was 43.8 million abortions in 2008 (Guttmacher Institute data)⁶. MAB has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare.⁷ Medical abortion comprises 16.5% of all abortions in the US, 25.2% of all abortions at or before 9 weeks of gestation¹, and based on data from 40 reporting areas sending data to the CDC, 30.8% of all abortions at or before 8 weeks gestation (2012 data).⁸ In 2011, approximately 239,400 medical abortions were performed, which was a 20% increase from 2008 data.⁹ Data show that in the most recently reported 12 months (September 29, 2014-September 28, 2015), (b) (4) Mifeprex tablets were distributed in the US (NDA 20687 SD # 650, Annual Report-15, submitted October 09, 2015). Further, the vast majority of practitioners in the US who provide medical abortion services use a regimen other than the FDA-approved one. In 2008, Wiegerinck et al published a survey of members of the National Abortion Federation which showed that only 4% of facilities were using the current FDA-approved regimen.¹⁰

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

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

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

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

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

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

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

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

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MAB is a choice that women have available in many areas, especially urban, in the US, although it should be noted that some geographical areas in the US have very limited availability of both the surgical and medical options or even one option for early pregnancy termination.

The primary advantages of having a MAB compared to a surgical abortion (SAB) are the following:

- Limited or no anesthesia
- Limited likelihood of any surgical intervention

Reviewer's Comment:

A very small number of physicians currently provide early medical terminations. In the most recent REMS update from the Applicant (stamp date June 3, 2015), the cumulative number of certified prescribers since 2000 is only (b) (4). Between May 1, 2012 and April 30, 2015, the number of new prescribers was (b) (4) and the number of prescribers ordering Mifeprax was (b) (4) during this 3-year period. The number of healthcare providers that are performing early SAB is not documented.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Because this submission did not rely on datasets from any of the clinical trials, no FDA inspections were performed at clinical sites. The authors of the numerous articles, however, have published widely in peer-reviewed medical journals.

3.2 Compliance with Good Clinical Practices

This submission relies on findings from the published medical literature. The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent.

3.3 Financial Disclosures

None were submitted or required.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

On March 10, 2016, a separate supplement approved the packaging of a single 200 mg tablet of mifepristone compared to the current 3 tablets in a blister pack. Each packet will have an individual barcode.

Reviewer comment:

The approval of single tablet packaging should make recording the barcode of the mifepristone tablet in the patient record (as provided in the REMS) easier as the new proposed dosing regimen uses only one 200 mg mifepristone tablet compared to the previously approved regimen of three tablets.

(b) (6), reviewed the PLR conversion of the label. Her review, dated January 11, 2016 states the following:

“No changes have been made in the approved chemistry, manufacturing and controls. The approved 200 mg tablet will be used. This review evaluates the PLR conversion of the labeling. Sections 3, 11, and 16 of the PLR labeling, and the Highlights of Prescribing Information, have been evaluated from a chemistry perspective.

Overall Evaluation: Acceptable. The labeling provided in Section 3, Section 11, and Section 16, and the Highlights of Prescribing Information, is identical in content to the approved information. The PLR conversion labeling, therefore, is acceptable from a chemistry perspective. The PLR label also corresponds to the content and format required in 21 CFR 201.57.

Reviewer comment:

We agree with the conclusions in the CMC review of the PLR conversion of the label.

4.2 Clinical Microbiology

The chemistry (CMC) reviewers determined that a microbiology review was not needed for this efficacy supplement.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology review by (b) (6), dated March 2, 2016. No preclinical data were submitted for this efficacy supplement. The reviewer's only recommendations were labeling changes. His comments were conveyed to the Sponsor.

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Per (b) (6) review, the supplement is approvable from a Pharmacology/Toxicology standpoint.

4.4 Clinical Pharmacology

The Clinical Pharmacology review by (b) (6) concluded with the following recommendation:

“(b) (6), (b) (6) has reviewed the available clinical pharmacology information in relation to the newly proposed regimen for Mifeprax[®]. We find the application to be acceptable from a Clinical Pharmacology perspective, provided that an agreement on the language in the package insert is reached between the Sponsor and the Division.”

No postmarketing commitments or requirement are recommended.

4.4.1 Mechanism of Action

The original approved label states:

“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. The termination of pregnancy results.

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

4.4.2 Pharmacodynamics

No new studies were submitted with this Application. See the original approved label.

4.4.3 Pharmacokinetics

(b) (6) review states the following:

The pharmacokinetics (PK) of 200 mg mifepristone tablet has not been characterized in women. However, the PK data of 200 mg mifepristone tablet in men are available (1996 study): the mean maximum concentration (C_{max}) (\pm standard error) = 1.77 (\pm 0.23) mg/L, the mean time to reach C_{max} (T_{max}) = 0.81 (\pm 0.16) hour, and the mean area-under-the curve (AUC) = 25.8 (\pm 2.2) mg-h/L. While the effects of sex on the disposition of mifepristone have not been evaluated using Mifeprax[®], no sex differences in PK of mifepristone were seen with 300 mg mifepristone in a different NDA review (Korlym[™], NDA 202107, Clinical Pharmacology review). Therefore, Section 12.3 of the proposed label in a PLR format should include the available PK data of mifepristone 200 mg tablet.

Cytochrome P450 3A4 (CYP3A4) plays an important role in the metabolism of mifepristone. Therefore, concomitant intake of CYP3A4 inducers with mifepristone

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is anticipated to have a significant effect on the disposition of mifepristone. However, the Sponsor did not conduct any *in vivo* studies to evaluate the effect of CYP3A4 inducers on the PK of Mifeprax[®]. Although the lowest effective therapeutic margin of mifepristone for termination of pregnancy has been not characterized clearly, the use of misoprostol in the regimen for Mifeprax[®] contributes to efficacy for inducing termination of pregnancy. In addition, concomitant intake of CYP3A4 inducers does not appear to affect the systemic exposure of misoprostol. In the proposed new regimen, another dose of misoprostol can be administered following day 7 to 14 of post-treatment of mifepristone if termination of pregnancy does not occur.

In summary, the contribution of misoprostol in termination of pregnancy and additional dosing option of misoprostol may compensate the possibly diminished efficacy of Mifeprax[®] in the users of CYP3A4 inducers. However, the labeling information should include the practical clinical guidance for the subject who has been exposed to CYP3A4 inducers.

Reviewers comments:

- **We agree with the Clinical Pharmacology conclusions and recommendations made by (b) (6).**
- **Within the last 10 years, administration of oral mifepristone followed by buccal misoprostol for early medical abortion has become the standard of care for MAB in many countries, including the US. This is based on 1) the PK profile of different doses and routes of administration for misoprostol, and 2) many clinical trials comparing the efficacy and safety of different dosing regimens.**

From Chen and Creinin (2015)¹²:

“With buccal administration, misoprostol is held in the buccal pouch between the teeth and gums for 30 minutes before swallowing any remaining tablets. Buccal misoprostol is slowly absorbed, unlike oral misoprostol, which is rapidly absorbed and undergoes extensive first-pass metabolism. After a dose of oral misoprostol, plasma misoprostol acid levels peak quickly at 30 minutes and decrease rapidly by 120 minutes. In contrast, after buccal administration, plasma misoprostol acid levels rise gradually to peak concentration after a median time of 75 minutes and fall slowly over several hours.”

¹² Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015;126(1):12-21.

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The PK profile of vaginal misoprostol is very similar to that of buccal misoprostol. These pharmacological differences between vaginal and buccal misoprostol do not have a clinically meaningful effect on the efficacy at different gestational weeks and the adverse event profile for the combination of mifepristone and misoprostol for early medical abortion. Those routes with rapid and significant absorption (e.g., sublingual) also have high efficacy (ACOG Bulletin¹). This review, however, focuses primarily on the new dosing regimen proposed by the Applicant with some supportive data from studies that used vaginal and sublingual misoprostol.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were many studies that provided data for this NDA review. The original US trial that was reviewed for the Mifeprex approval in 2000 was performed over 20 years ago in 1994-95. Subsequently, there has been 20 years of experience with MAB, guidelines from professional organizations here and abroad, and clinical trials that have been published in the peer-reviewed medical literature. This review focuses on the information submitted by the Applicant for the change in the dosing regimen and follow-up.

For a complete list of all sources of information, see the extensive list of references in Appendix 9.6 at the end of this review.

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NDA 020687/S-020- Mifeprex**Table 1: List of Major Studies Reviewed**

USA	International
Gatter 2015 ¹³ , retrospective	Louie 2014 ¹⁴ , Azerbaijan, prospective
Ireland 2015 ¹⁵ , retrospective	Ngoc 2014 ¹⁶ , Vietnam, prospective
Chong, 2015 ¹⁷ , prospective single-arm	Raymond 2013 ¹⁸ , International, including US, retrospective
Winikoff 2012 ¹⁹ , prospective	Goldstone 2012 ²⁰ , Australia, retrospective
Perriera 2010 ²¹ , prospective	Boersma 2011 ²² , Curacao, prospective
Winikoff 2008 ²³ , RCT*	Middleton 2005 ²⁴ , prospective
Creinin 2007 ²⁵ , prospective	Spitz 1998 ²⁶ , single arm trial

¹³ Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

¹⁴ Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. *Eur J Contracept Reprod Health Care* 2014;19(6):457-464.

¹⁵ Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. *Obstet Gynecol* 2015;126:22-8.

¹⁶ Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. *Obstet Gynecol* 2014;123:88-95.

¹⁷ Chong E, Frye LJ, Castle J, Dean G, Kuehl L, Winikoff B. A prospective, non-randomized study of home use of mifepristone for medical abortion in the US. *Contraception* 2015;92:215-291.

¹⁸ Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.

¹⁹ Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012;120:1070-6.

²⁰ Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. *Med J Austral* 2012; 197: 282-6.

²¹ Perriera LK, Reeves MF, Chen BA, Hohmann HL, Hayes J, Creinin MD. Feasibility of telephone follow-up after medical abortion. *Contraception* 2010;81:143-149.

²² Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011;16:61-6.

²³ Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008;112(6):1303-1310.

²⁴ Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005;72:328-32.

²⁵ Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Medical Abortion at the Same

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Source: compiled by clinical reviewers. *Randomized controlled trial.

Reviewer's comment:

Table 1 above lists the major studies and review articles covering over 45,000 women who had an early MAB through 70 days gestation. Both retrospective and prospective studies were found to be valuable for this review. There are additional studies submitted by the Applicant that are not quoted or reviewed primarily because they did not use a dosing regimen relevant to that proposed by the Applicant or did not contain information pertinent to the other requested changes (e.g., less restrictive follow-up requirements or gestations through 70 days) in the NDA supplement. In some cases, studies that used variants of the proposed regimen were considered because PK, PD and clinical data indicate the relevance of data on vaginally-administered misoprostol, and because lower doses and certain other routes of administration of misoprostol are expected to have lower or similar levels of effectiveness.

5.1.1 Submissions during the Review Process

During the course of the review, the Applicant submitted additional supportive articles from the peer-reviewed medical literature, and provided more detailed data from previously submitted articles based on direct communication with the authors. Further, the Applicant submitted changes to some of the original proposals. Below in Table 2 is a list of the clinical submissions to the NDA after the initial submission dated May 18, 2015.

Time (MAST Study Trial Group). Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion a randomized controlled trial. *Obstet Gynecol* 2007;109:885-894.

²⁶ Spitz IM, et al. Early Pregnancy Termination with Mifepristone and Misoprostol in the United States. *NEJM* 1998;338(18):1241-47.

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Table 2 Clinical Submissions during the Course of the Review

Item	Submission Type, Date
Additional supportive articles More detailed data from previously submitted articles	Amendment # 3, dated 9/23/2015 Amendment # 4, dated 10/13/2015 Amendment # 5, dated 11/16/2015 Amendment # 6, dated 12/8/2015
Additional supportive documents on patient counseling	Follow-up to 1/27/2016 teleconference, dated 2/2/2016
Additional supportive articles	Amendment # 8, dated 2/25/2016
Proposed Additional Changes	
REMS amendment, Revised REMS Supporting Document Additional supportive articles	Amendment # 2, dated 7/16/2015
REMS modification	Dated 11/4/2015
Labeling: (b) (4) Indication Statement	Amendment # 4, dated 10/13/2015
Labeling changes: (b) (4) the proposed new dosage regimen (b) (4) (b) (4) (b) (4)	Follow-up to 1/27/2016 teleconference, dated 2/15/2016, Also in Amendment # 9, dated 2/25/2016
Labeling: changes to Sections 2.4, 5.2, 6.1, 7, 8.1, 8.2, 8.6, 12.3, 14	Amendment # 7, dated 2/23/2016
Labeling changes: revise indication statement to state “through 70 days gestation	Amendment # 9, dated 2/25/2016
Labeling: changes to Sections 2.3, 6.1 and 14	Amendment # 10, dated 3/17/2016
REMS documents	Amendment #11, dated 3/21/2016

Source: Reviewer table.

5.2 Review Strategy

This is a joint review by two medical officers: (b) (6) reviewed the efficacy data and (b) (6) reviewed safety data and related issues. Other sections are jointly completed.

Within the last 10 years, use of buccal misoprostol with mifepristone for MAB has become commonplace. However, the published literature did not contain abundant information about medical abortion outcomes with buccal misoprostol at the time of the

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original NDA review. In this review, we summarize clinical outcomes and adverse effects of medical abortion regimens consisting of oral mifepristone 200 mg followed in 24-48 hours by buccal misoprostol 800 mcg in pregnancies through 70 days of gestation.

5.2.1 Discussion of Individual Studies/Clinical Trials

Information and findings from individual clinical trials and reviews in the published medical literature, websites, the Applicant and other sources are discussed in different sections throughout this review. As acknowledged during pre-submission discussions between the Applicant and (b) (6) and as is typical for literature-based submissions, original datasets from the trials that are cited were not available for submission in this supplement.

6 Review of Efficacy

Efficacy Summary

This summary lists the final conclusions based on review of the data. Not all of the conclusions, regarding covariates such as ethnicity, parity, previous abortion, are specifically addressed in labeling, but the reviewers believe that it is important to show that we evaluated many different aspects and potential risk factors for safe and effective MAB:

- Medical termination of pregnancies through 70 days gestation is safe and effective and should be approved using the new proposed regimen.
- The original approved dosing regimen remains safe and effective but the new proposed dosing regimen is effective and should be approved for use in gestations through 70 days (10 weeks) gestation.
- 2015 Chen-Creinin review¹² of over 33,800 MABs concluded that regimens with a 24-hour time interval between mifepristone and buccal misoprostol administration are slightly less effective (94.2% success) compared to those with a 24-48-hour interval (96.8% success).
- 2013 Raymond review¹⁸ of over 45,500 MABs using oral mifepristone 200 mg and various misoprostol doses concluded that the effectiveness decreases when:
 - misoprostol is taken orally compared to the three other routes of administration (buccal, sublingual, or vaginal)
 - the gestational age increases
 - the mifepristone-misoprostol interval is less than 24 hours
 - the total misoprostol dose is 400 mcg or less
- Efficacy in the adolescent population is the same or slightly better compared to non-adolescent women.

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- Efficacy outcomes do not appear to be related to other baseline characteristics including age, race, body weight, gravidity and previous spontaneous abortions. (Spitz data²⁶ and many subsequent studies)
- Data from the original US trial (1994-95; Spitz 1998²⁶) showed lower efficacy rates with the originally approved Mifeprex dosing than is reported in a large number of subsequent trials using different mifepristone-misoprostol dosing regimens for early MAB. There does not appear to be any change in the safety profile.
- Raymond (2013 systematic review¹⁸) found no significant association between abortion failure rates and the timing of the follow-up evaluation.
- Over 30% of women will completely expel the products of conception within 4-5 hours of taking the misoprostol for MAB with gestations of 57-70 days (Winikoff 2012¹⁹); this finding supports the proposal to allow women to choose the timing of (within the labeled range) and where to take the misoprostol.
 - Data from the original NDA review showed occurrence of a successful (complete) MAB occurred in ≤ 4 hours after misoprostol administration in 45-46% of women up to 56 days gestation and 34.9% of women at 57-63 days gestation.
- Home administration of misoprostol is efficacious, practical, and safe (see Safety Section)

Reviewer's overall comment:

Compared to the current Mifeprex approved label and regimen, the Applicant has requested less restrictive measures for location and timing of misoprostol administration and follow-up measures for early MAB. We believe that a regimen that includes these less restrictive measures is equally safe and effective, while offering women greater convenience and providing a less burdensome procedure for patients and providers.

6.1 Indication

In the initial submission of this efficacy supplement, the proposed new indication was the following: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (b) (4)" In Amendment # 9, submitted on February 25, 2016, the Applicant proposed (b) (4) the gestational age through 70 days.

The proposed new modified regimen uses buccal (not oral) misoprostol administered 24-48 hours after taking a lower dose, 200 mg instead of 600mg, of oral mifepristone. The labeled dose of misoprostol is increased compared to the current approved regimen, from 400 mcg to 800 mcg. (b) (4)

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(b) (4)

These requests were thoroughly reviewed by the Agency and we believe the product is safe and effective for the indication, which reads:

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

6.1.1 Methods

There were numerous articles from the peer-reviewed medical literature that were submitted by the Applicant. Articles were also cited in three letters sent to CDER Center Director Janet Woodcock, MD from 1) ACOG, 2) a group of academic professionals and women's health non-profit organizations, and 3) thirty professional and academic organizations, all of which requested changes to the Mifeprex labeling and REMS. All relevant publications cited in those three letters were also submitted by the Applicant for our review. The articles and sources of data used for this review are listed in the Reference List in Appendix 9.6 at the end of this review.

The various studies noted in the articles had slightly different designs, inclusion criteria, dosing regimens and endpoints for safety and efficacy. The review focus is on clinical trials and follow-up methods for early medical abortion, including gestations through 70 days (10 weeks).

6.1.2 Demographics

Many of the trials were randomized and some were blinded to the actual dose of the two drugs that were administered. The route of misoprostol administration could not be easily blinded. Although there may have been some small differences in the demographic data for the different arms, it is doubtful that demographic differences such as race or ethnicity are clinically meaningful in relation to the safety and efficacy of medical abortion.

6.1.3 Subject Disposition

Most of the studies noted the number of women who were lost to follow-up and did not count them in the efficacy analysis. All women with any available safety data were included in the safety analyses. See Safety Section for further discussion.

6.1.4 Analysis of Primary Endpoint(s)

The studies analyzed for data used in this NDA review almost universally defined their primary efficacy endpoint as expulsion of the pregnancy from the uterus without need for any surgical evacuation or procedure for any reason (including patient request).

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6.1.5 Analysis of Secondary Endpoints(s)

In addition to the final outcome of MAB success or lack of success (i.e., surgical or medical intervention needed), there are intermediate outcomes:

- Incomplete abortion: pregnancy no longer ongoing, but only partial or non-expulsion of the products of conception has occurred
- Ongoing pregnancy based on fetal heartbeat and/or growth

In the case of incomplete expulsion but where the pregnancy is no longer ongoing, there are in the US several safe options available to the healthcare provider and the patient:

- Expectant management (in many cases, complete expulsion will occur spontaneously given additional time)
- Additional dose of misoprostol
- Minor surgical procedure such as a vacuum aspiration in the clinic/office
- Surgical procedure under anesthesia such as a dilation and curettage (D&C)

For ongoing pregnancies following the initial MAB procedure, typically one of the surgical procedures is performed.

In addition to these two intermediate outcomes, there are other cases in which a surgical intervention might be performed:

- Intervention because of bleeding or other aspect of the patient's condition: the healthcare provider judges that surgical intervention is indicated
- Patient request: the patient requests surgical intervention for any reason

6.1.6 Proposal for a New Dosing Regimen

There are five major changes proposed by the Applicant in this supplement for which efficacy data will be discussed. The changes are interrelated and, in general, the same studies usually provide evidence to support multiple changes, although data from a given study may be more or less pertinent to a specific change (e.g., extending the approved gestational age, home administration of buccal misoprostol, etc.).

Summary of changes to dosing regimen, indication, and follow-up initially requested by the Applicant in the NDA Supplement:

1. **Addition of a new dosing regimen of Mifeprex 200 mg orally followed by the buccal administration of 800 mcg misoprostol at 24-48 hours instead of 48 hours**
2. **Increase in gestational age from (b) (4)**
3. **Option to administer misoprostol outside of the clinic**

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4. **Option that a repeat dose of misoprostol may be used if needed for women using the new proposed dosing regimen**
5. **Follow-up timing and methods: follow-up is needed at 7-14 days after Mifeprex administration; the specific nature and timing of the follow-up to be agreed upon by the (b) (4) and patient. The current approved label states: “Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex.”**

Discussion and analysis of the data supporting the five changes follows in five individual sections.

1. **Proposal of a new dosing regimen that:**
 - 1) **decreases the oral dose of Mifeprex from 600 mg to 200 mg orally,**
 - 2) **increases the misoprostol dose from 400 mcg orally to 800 mcg misoprostol administered buccally, and**
 - 3) **revises the interval between Mifeprex and misoprostol dosing from 48 hours to “24-48 hours.”**

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Background on some dosing data and US practices:

There is ample medical evidence that the currently approved dose regimen (oral mifepristone 600 mg followed 2 days later with oral misoprostol 400 mcg) is safe and efficacious up to 49 days gestation. It was approved in September 2000 based on the US clinical trial of 1994-95 and two French trials. After 1995, however, more studies gradually became available using lower doses of mifepristone and different doses and routes of administration for misoprostol. These newer data were not submitted to or considered in the original NDA review. Studies also showed that with lower doses (< 600 mg) of oral mifepristone followed by oral misoprostol 400 mcg, the treatment success rate is greater than 95% up to 49 days gestation.

It is difficult to tell how many MABs in the US actually used the FDA-approved dosing regimen following the 2000 approval. It is clear that many clinics and individual practitioners did not. For example, from 2001 to March 2006, Planned Parenthood Federation of America (PPFA) health centers throughout the United States provided medical abortions principally using a regimen of oral mifepristone 200 mg, followed 24–48 hours later by 800 mcg misoprostol administered vaginally at home.²⁷ Of note, PPFA has been and continues to be the largest provider of MAB services in the US.

²⁷ Fjerstad M, Sivin I, Lichtenberg ES, Trussell J, Cleland K, Cullins V. Effectiveness of medical abortion

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Reviewer's comment:

The 2009 Fjerstad article²⁸ states that PPFA was a federation of 97 independent local affiliates operating 880 health centers throughout the US; roughly 300 of those centers provided medical abortion. So, within one year of the FDA Mifeprax approval, PPFA was using a dosing regimen (actual doses and routes of administration) very similar to that proposed in this efficacy supplement.

Meanwhile, from September 2003 to June 2005, there were four fatalities in the US and one in August 2001 in a Canadian clinical trial, all due to a sudden and rapid sepsis secondary to the bacteria *Clostridium sordellii*. The five cases were with early MAB (all around 7 weeks gestation) in women who had used 800 mcg vaginal misoprostol. By late March 2006, consideration of these fatal uterine infections led PPFA to 1) change the route of administration of the 800 mcg misoprostol from vaginal to buccal (or, much less commonly, oral) and 2) employ additional measures (sexually transmitted infection [STI] testing and treatment if positive, or use of prophylactic antibiotics) to minimize the risk of subsequent serious uterine infections. In July 2007, PPFA began requiring routine treatment with antibiotics for all medical abortions at their health centers.²⁸

Reviewer's comment:

As stated in currently approved labeling “No causal relationship between the use of Mifeprax and misoprostol and these events [serious and sometimes fatal infections and bleeding] has been established.” There is no clear evidence that the vaginal use of misoprostol causes infection, and no causal association has been identified between the cases of sepsis and vaginal administration of misoprostol. While labeling was revised in November 2004 and July 2005 to recommend that providers have a high index of suspicion in order to rule out serious infection and sepsis, the Agency did not consider there was sufficient evidence to justify recommending prophylactic antibiotics.

A 2006 article showed that in pregnancies greater than 49 days gestation, compared to oral administration of misoprostol, the bioavailability and efficacy with use of misoprostol is increased by vaginal, sublingual and buccal administration, avoiding first-pass metabolism by the liver.²⁹ Furthermore, a 2009 review of MAB³⁰ noted that:

“Consistent with other kinetic studies, clinical trials have demonstrated no change in efficacy when mifepristone doses are reduced from 600 to 200 mg. Multiple

with mifepristone and buccal misoprostol through 59 gestational days. Contraception 2009;80:282-6.

²⁸ Fjerstad M, Trussell J, et al. Rates of serious infection after changes in regimens for medical abortion. NEJM 2009;361:145-51.

²⁹ Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with prostaglandin analogue. Contraception 2006;74:66-86.

³⁰ Bartz B, Goldberg A. Medical Abortion. Clin Obstet and Gyn 2009; 52:140-50.

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clinical studies, including a 2004 Cochrane meta-analysis, reported that a regimen of 200 mg of oral mifepristone followed 24 to 48 hours later by 800 mcg of vaginal misoprostol results in complete abortion in 96% of cases at gestations of up to 63 days and that increasing the mifepristone dose to 600 mg does not improve efficacy.”

In a 2010 review article covering 25 years of the clinical development of mifepristone followed by a prostaglandin for MAB, Spitz³¹ noted similar conclusions:

“In the US, most investigators administer 200 mg rather than 600 mg mifepristone as many trials have shown equivalent results with these two dose schedules. A recent meta-analysis of four randomized controlled trials compared the two dose regimens. Endpoints were complete abortion, continuing pregnancy and side effects. The two doses [600 v. 200 mg mifepristone] result in similar rates of complete abortion with no difference in adverse events.”

Another change in clinical practice was related to the labeling stipulation that women return to the clinic/office two days after Mifeprex was administered to take the misoprostol dose. Many experts involved with termination of early pregnancies also advocated misoprostol self-administration at home to mitigate the time, travel and inconvenience of this additional visit.

In the US, the American College of Obstetricians and Gynecologists (ACOG), National Abortion Federation³², and PPFA currently all endorse the lower oral dose of mifepristone followed in 24-48 hours with misoprostol. According to the 2014 ACOG Practice Bulletin, the misoprostol route of administration may be oral, buccal, sublingual or vaginal; sublingual administration, however, has a more rapid absorption resulting in a higher incidence of adverse side effects.¹

European practice:

In December 2011, the International Federation of Obstetrics and Gynaecology (FIGO) published revised guidelines for the use of mifepristone and misoprostol for MAB up to 63 days, 64-84 days, and after 84 days (12 weeks) gestation.³³ The FIGO recommended regimens using 200 mg of oral mifepristone followed by 800 mcg of misoprostol administered vaginally, buccally, or sublingually. Up to 57-63 days gestational age, misoprostol is taken 24-48 hours after mifepristone. Per the review of data available to them, FIGO decided additional doses of 400 mcg misoprostol may be

³¹ Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. *Contraception* 2010;82:442–52.

³² National Abortion Federation Guidelines 2015.

³³ Faundes A. The combination of mifepristone and misoprostol for the termination of pregnancy. *Int J Gynecol Obstet* 2011;115:1-4.

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safely used depending on gestational age, and these combinations result in a complete termination in more than 95% of cases.

Similar guidelines using either vaginal, buccal, or sublingual misoprostol are endorsed by the World Health Organization (WHO), the United Kingdom Royal College of Obstetricians and Gynecologists³⁴, and a recent Cochrane Review (2011, Issue11).³⁵

Reviewer's Comment:

From the above discussion, it is clear that the standard of care in the US for early MAB has deviated from the FDA-approved dosing regimen. PPFA provides the largest number of medical abortions each year in the US and as early as 2001, was already using the regimen of 200 mg oral mifepristone followed 24-48 hours later by 800 mcg vaginal misoprostol.

There are a large number of studies and reviews that support the efficacy of the proposed new dose regimen through 63-70 days gestation. Efficacy was defined in these studies as a complete expulsion of the pregnancy without need for surgical intervention for any reason during the follow up period. The 2015 review by Chen and Creinin summarized clinical outcomes and adverse effects from 20 MAB studies including a total of 33,846 women using regimens consisting of 200 mg oral mifepristone followed by buccal misoprostol through 70 days gestation. All studies except two used 800 mcg misoprostol. Two studies (827 women) used 400 mcg buccal misoprostol. Six studies used a 24-hour time interval between mifepristone and buccal misoprostol administration and 14 used a 24-48 hour window for the dosing interval. The table below lists the 15 studies using the proposed doses (200 mg plus 800 mcg) with a 24-48 hour dosing interval.

³⁴ Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline Number 7. 3rd ed. London (UK):RCOG Press 2011.

³⁵ Kulier R, Kapp N, et al. Medical methods for first trimester abortion (Review). The Cochrane Library 2011, Issue 11:1-126.

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Table 3: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later - US Studies

Study & Year	Design, Location	Gestation (maximum days)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Middleton 2005 ²⁴ US	Prospective	56	24-48	216	94.9
Winikoff 2008 ²³ US	Prospective	63	24-36	421	96.2
Fjerstad 2009 ²⁷ US	Retrospective	59	24-48	1,349	98.3
Grossman 2011 ³⁶ US - Clinic Mife v. Tele-med	Prospective	63	24-48	449	Clinic: 96.9% Telemed: 98.7%
Winikoff 2012 ¹⁹ US	Prospective	57-70	24-48	629	93.2
Gatter 2015 ¹³ US	Retrospective	63	24-48	13,373	97.7
Chong 2015 ¹⁷ US	Prospective	63	24-48	357	96.7
TOTALS	7 Studies	56-70 days	24-48 hr	16,794	97.4

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

³⁶ Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.

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Table 4: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later- Non- US Studies

Study &Year/Country	Design, Location	Gestation (maximum)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Alam 2013 ³⁷ Bangladesh	Prospective	63	24	629	92.7
Blum 2012 ⁷⁰	Prospective	63	24	210	92.9
Boersma 2011 ²² Curacao	Prospective	70	24-48	307	97.7
Chai 2013 ³⁸ Hong Kong	Prospective	63	48	45	95.6
Dahiya 2012 ³⁹ India	Prospective	50	24	50	92
Chong 2012 ⁴⁰ Georgia, Vietnam	Prospective	63	36-48	560	96.4
Giri 2011 ⁴¹ Nepal	Prospective	63	24	95	93.6
Goldstone 2012 ²⁰ Australia	Retrospective	63	24-48	11,155	96.5
Louie 2014 ¹⁴ Azerbaijan	Prospective	63	24-48	863	97.3
Ngo 2012 ⁴² China	Retrospective	63	36-48	167	91.0
Ngoc 2011 ⁴³ Vietnam	Prospective	63	24	201	96.5
Ngoc 2014 ¹⁶ Vietnam	Prospective	63	24-48	1,371	94.7
Olavarietta 2015 ⁸⁵ Mexico	Prospective	70	24	884	98.2
Pena 2014 ⁴⁴ Mexico	Prospective	70	24-48	971	97.3

³⁷ Alam A, Bracken H et al. Acceptability and Feasibility of Mifepristone-Misoprostol for Menstrual Regulation in Bangladesh. *International Persp on Sexual and Reprod Health* 2013;39(2):79-87.

³⁸ Chai J, Wong CY, Ho PC. A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation. *Contraception* 2013;87:480-5.

³⁹ Dahiya K, Ahuja K, Dhingra A et al. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. *Arch Gynecol Obstet* 2012; 285: 1055-8

⁴⁰ Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. *Contraception* 2012;86:251-6.

⁴¹ Giri A, Tuladhar H et al. Prospective study of medical abortion in Nepal Medical College- a one year experience. *Nepal Medical Coll J* 2011;13(3):213-15.

⁴² Ngo TD, Park MH, Xiao Y. Comparing the WHO versus China recommended protocol for first trimester medical abortion: a retrospective analysis. *Int J Womens Health* 2012;4:123-7.

⁴³ Ngoc NTN, et al. Comparing two early medical abortion regimens: mifepristone+misoprostol vs. misoprostol alone. *Contraception* 2011;83:410-17.

⁴⁴ Pena M, Dzuba IG, Smith PS, et al. Efficacy and acceptability of a mifepristone-misoprostol combined

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Sanhueza 2015 ⁴⁸ Mexico	Prospective	70	24-48	896	93.3
TOTALS	15 Studies	56-70 days	24-48 hrs	18,425	96.1%

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

Reviewer's comments:

The data above in Table 3 and Table 4 from ~16,800 US women and ~18,400 non-US women in clinical studies of MAB through 70 days gestation with success rates of 97.4% (US) and 96.1% (non-US) strongly support the proposed new dosing regimen and the extension of the acceptable gestational age. The number of US and non-US studies, the number of evaluable women, and the overall complete abortion rates (termination with no surgical intervention) will be described in the efficacy table in Section 14 CLINICAL STUDIES in the new approved label. Additional discussion on increasing the gestational age through 70 days follows in the next major section.

Precise timing of the administration of misoprostol has not been shown to result in a higher success rate which is why the majority of the above studies allowed a range of hours between the mifepristone dose and misoprostol dose rather than one set time between the two drugs. The 2013 Raymond systematic review¹⁸ of 87 studies that exclusively used a mifepristone 200 mg oral dose in over 45,000 women, followed by varying doses and routes of administration of misoprostol, concluded that if the mifepristone-misoprostol interval is < 24 hours, the procedure is less effective compared to an interval of 24-48 hours.

Another study⁴⁵ also looked at the question of the mifepristone-misoprostol interval. The authors conducted a systematic review of randomized controlled trials published from 1999 to 2008 to assess the evidence for a shorter mifepristone and misoprostol administration interval for first trimester medical termination. Searching strategy included MEDLINE, EMBASE, CLINAHL and Cochrane Library. The primary outcome measure was complete abortion without the need for a surgical procedure. "Five randomized controlled trials (RCTs) compared the efficacy of mifepristone-misoprostol administration intervals between 0 and 72 hours in 5,139 participants. The complete abortion rates varied between 90% and 98%. Although the meta-analysis of pooled data of all five RCTs showed no statistically significant difference in efficacy between

regimen for early induced abortion among women in Mexico City. *Int J Gynaecol Obstet* 2014;127:82-5.

⁴⁵ Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. *Contraception* 2010;81(4):269-74. doi: 10.1016/j.contraception.2009.09.007. Epub Oct 29, 2009.

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the shorter and longer dosing intervals, there was a trend toward slightly lower success rates with administration intervals < 8 hours.” This study supports the finding that the proposed regimen is effective with the 24-48 hour flexible interval. Labeling will indicate that the regimen may not work as well if the misoprostol is taken earlier than 24 hours after Mifeprex.

Reviewer’s Final Recommendation:

The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved; there are sufficient data from the medical literature with over 35,000 women supporting the regimen’s efficacy (termination without any additional surgical intervention) as being in the 91-98% range.

6.1.7 Increase in gestational age from 49 days to 70 days**Original NDA review:**

The US clinical trial³¹ was conducted from September 1994 to September 1995 and treated 2,121 women. A total of 2,015 women (95%) returned at the 14-day follow-up visit. The trial categorized women into three groups based on gestational age at the time of procedure, and evaluated the rates of “Success” (a complete pregnancy termination without use of any additional doses of misoprostol or surgical intervention), and the rates of “Failure” (with four sub-categories of incomplete abortion, ongoing pregnancy, intervention for medical reason, and intervention solely because of patient request). The success and failure data are shown in Table 5.

Table 5: Original NDA Efficacy Results

OUTCOME	≤ 49 Days N= 827 (%)	50-56 Days N= 678 (%)	57-63 Days N= 510 (%)
Success (mifepristone + misoprostol)	762 (92)	563 (83)	395 (77)*†
Failure (any surgical intervention for any reason) N (%)			
Total failures	8%	17%	23%*†
Incomplete abortion	39 (5)	51 (8)‡	36 (7)
Ongoing pregnancy	8 (1)	25 (4)*	46 (9)* §
Medical indication for intervention	13 (2)	26 (4)‡	21 (4)‡
Patient’s request for intervention	5 (0.6)	13 (2)	12 (2)‡

*P<0.001 for the comparison with the ≤ 49-days group.

†P= 0.02 for the comparison with the 50 to 56-days group.

‡ 0.001 ≤ P<0.03 for the comparison with the ≤ 49-days group.

§ P<0.001 for the comparison with the 50 to 56-days group.

Source: Modified from Table 1, pg 1243 in the Spitz NEJM article (1998).

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Reviewer's comments:

Looking at the results in the table above, it is reasonable that the approved use was only for women in the first 49 days' gestation, given the 8% "failure rate" in this subgroup, compared to 17% and 23% failure rates for the longer gestations. It is important to note that failure was defined as any case requiring surgical intervention for any of the following reasons:

- incomplete abortion (incomplete expulsion)
- documented ongoing pregnancy
- medical reasons (usually heavy vaginal bleeding with or without retained products of conception)
- patient request (usually for bleeding)

As has been pointed out, since the US trial data used for the FDA approval of Mifeprex, given the experience and data gained in the last 20 years from millions of women in the US and abroad, the success rates and overall outcomes are very different. Currently, when a "failure" occurs, using the original definition, options that are now commonly available include the following:

- expectant management (wait and see) in the case of an incomplete abortion (i.e., pregnancy terminated but not fully expelled)*
- medical treatment for bleeding, pain and other common symptoms
- clinical evaluation with the use of 1) office ultrasound and/or 2) hCG data determined by rapid, sensitive urine and/or serum testing*
- additional doses of misoprostol for an incomplete abortion*
- less invasive surgical intervention (vacuum aspiration) in the clinic/office instead of a D&C under anesthesia in an operating room
- continuing the pregnancy (although the medical recommendation is to proceed to a surgical abortion in such a case, we acknowledge that a woman could potentially decide to continue the pregnancy)

* per protocol, these options were NOT available in the original US trial

It is also evident that the proposed new dosing regimen is considerably more effective for all gestations through 70 days [see data and discussion that follows for 57-63 and 64-70 days gestation], especially when compared to the original data using the FDA-approved regimen which had "success" rates of only 83% and 77% at 50-56 and 57-63 days gestation, respectively.

Current evidence for increasing the gestational age to 70 days

Current evidence demonstrates that the new proposed medical abortion regimen is effective for women in the range of 57-63 days and 64-70 days of gestation. A 2015

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systematic review identified six published studies that recorded data on outcomes of medical abortions performed during gestational Days 64-70.⁴⁶

The published studies were conducted in the United States, UK, Mexico, Curaçao, Vietnam, and the Republic of Georgia. All subjects were treated as outpatients between 2007 and 2015. The older UK study evaluated 127 women who were at 64-70 days gestation and treated with 200 mg oral mifepristone followed by 800 mcg vaginal misoprostol.⁴⁷

Reviewer comment:

We evaluated the data separately for 57-63 and 64-70 days of gestation. The following two tables show the efficacy data for 57-63 and 64-70 days gestation (also known as Week 9 and Week 10).

⁴⁶ Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70days gestation. *Contraception* 2015;92:197-9.

⁴⁷ Gouk EV, et al. Medical termination of pregnancy at 63-83 days gestation. *British J Obstet Gyn* 1999;106:535-539.

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NDA 020687/S-020- Mifeprex**Table 6: MAB Efficacy Outcome 57-63 Days Gestation**

Study	Enrolled N	Followed N	Success N (%)	Ongoing Pregnancy N (%)	Lost to Follow up %	Comment
Winikoff ²³ 2008 US-	132	115	109 (94.8)	2 (1.7)	13.0%	* Proposed Dosing
Winikoff ¹⁹ 2012 US	379	325	304 (93.5)	10 (3.1)	14.2%	* Proposed Dosing
Gatter ¹³ 2015 US	1527	1286	1228 (95.5)	21 (1.6)	15.8%	* Proposed Dosing
Sanhueza ⁴⁸ 2015 Mexico City	196	190	171 (90.0)	6 (3.2)	3.1%	* Proposed dosing
Boersma ²² 2011** Curacao	105	95	91 (95.8)	2 (2.1)	9.5%	*Proposed dosing @ 24- 36 hr @ home
Pena ⁴⁴ 2014 Mexico City	177	171	164 (95.9)	2 (1.2)	3.4%	* Proposed dosing
Chong ⁴⁰ 2012 Viet Nam, Georgia	86	85	79 (92.9)	2 (2.4)	1.2%	*Proposed dosing 36-48 hr
	81	81	77 (95.1)	2 (2.5)	0%	400 mcg buccal @ 36- 48 hr
Bracken ⁴⁹ 2014 4 countries-	389	382	362 (94.8)	7 (1.8)	1.3% (2 women withdrew)	400 mcg sublingual @ 24-48 hr
TOTAL	3,072	2,730	2,585 (94.7)	54 (2.0%)	11.1%	

*Mifepristone oral 200 mg followed in 24-48 hour range with misoprostol buccal 800 mcg.

**Boersma study reported the interval from 50-63 days without further breakdown.

Source: Data from published studies.

⁴⁸ Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015;22:75-82.

⁴⁹ Bracken H ,Dabash R, Tsertsvadze G et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. *Contraception* 2014;89(3):181-6.

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Reviewer comments:

Although the Chong and Bracken studies do not use the exact proposed dosing regimen, it is felt that their efficacy results are relevant because both used a lower dose of misoprostol, which, if anything, would have been expected to provide lower efficacy.

After careful review of the above eight studies, we find the following results. A combined total of 3,072 women were treated at 57-63 days of gestation, with 2,730 (88.9%) providing outcome data. Of these women, 2,585 (94.7%) had a complete medical abortion (pregnancy termination without any surgical intervention), and 54 (2.0%) had ongoing pregnancies. This successful treatment rate is better (94.7% compared to 92.1%) than the rate in the data on which the 2000 FDA Mifeprex approval was based. The data are sufficient and acceptable for extending the approval of Mifeprex up to at least 63 days gestation.

The numbers here do not exactly match the results shown in the efficacy table for 57-63 gestational days that are in Section 14 CLINICAL STUDIES in the new approved label, which is limited to studies using the identical dosing regimen to that proposed in this supplement. The number of evaluable women here is higher because the Chong and Bracken data are included, as noted above in the comment. The label, however, states the same conclusion of a 94.7% complete medical abortion rate and a 2% ongoing pregnancy rate.

Data for 64-70 days gestation are found in the next table.

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Table 7: MAB Efficacy Outcome 64-70 Days Gestation

Study	Enrolled N	Followed N	Success N (%)	Ongoing Pregnancy N (%)	Lost to Follow up %	Comment
Winikoff ¹⁹ 2012	350	304	282 (92.8)	9 (3.0)	13.1	*Proposed dosing
Sanhueza ⁴⁸ 2015	150	147	134 (91.2)	5 (3.4)	2.0	* Proposed dosing
Boersma ²² 2011†	26	26	25 (96.2)	1 (3.8)	0	Proposed dosing @ 24- 36 hr @ home
Pena ⁴⁴ 2014	2	2	2 (100)	0 (0)	0	* Proposed dosing
Chong ⁴⁰ 2012 RCT	1	1	1 (100)	0 (0)	0	* Proposed dosing @ 36-48 hr
	6	6	6 (100)	0 (0)	0	400 mcg buccal
^Y Gouk ⁴⁷ 1999 UK- misoprostol in hospital	127	127	120 (94.5)	7 (5.5)	0	800 mcg vaginal @ 36-48 hr
Bracken ⁴⁹ 2014	325	321	295 (91.9)	7 (2.2)	1.2	400 mcg sublingual @ 24-48 hr
TOTAL	987	934	865 (92.6)	29/934 (3.1)	53/987 (5.4)	

*Mifepristone oral 200 mg followed in 24-48 hour range with misoprostol buccal 800 mcg.

^YThe Gouk study in 1996-97 included 253 women at 63-83 days gestation (Weeks 10-12).

Source: Table modified with data from published studies. See Abbas D et al. Contraception [MAB through 70 days gestation] 92 (2015):197-199.

Reviewer comments:

Use of the Chong and Bracken data is discussed above. Although the Gouk regimen used a different route of administration for misoprostol, the effectiveness of the vaginal route appears to be similar to that of the buccal route; therefore, these data are considered relevant. Data on sublingual administration of misoprostol may be less generalizable due to the different pharmacokinetic (PK) profile and higher AE frequency compared to buccal

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administration. Also, see Section 4.4.3 Pharmacokinetics and the Cross Discipline Team Leader review.

The abortion success rates shown above from seven studies are comparable to (and in several studies, greater than) the success rates for medical abortion in the initial 2000 decision for Mifeprex up to 49 days gestation. The proportion of subjects with complete success without any medical or surgical intervention in the US pivotal trial that supported the original approval was 92.1%, as shown in Table 5, in 827 women encompassing all gestational weeks up to 49 days. The data in the above two tables include 3,072 women treated at 57-63 days gestation and 987 women at 64-70 days gestation. We believe that this comprises a sufficient number of women in each gestational week upon which to make a clinical decision, and that the overall 94.7% and 92.6% success rates are acceptable for approval.

The data here clearly establish the efficacy of medical abortion with mifepristone and misoprostol through 70 days gestation. At least two Gynuity Health studies of outpatient medical abortion through 70 days are ongoing, so more information from clinical studies will be available in the future.

It is also worth noting that in November 2015, the National Medical Committee of PFFA approved medical abortion through 70 days, so this is currently their standard of care.

Reviewer's Final Recommendation:

The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved for use through 70 days gestation (10 weeks from the first day of the LMP).

6.1.8 At-home Administration of Misoprostol

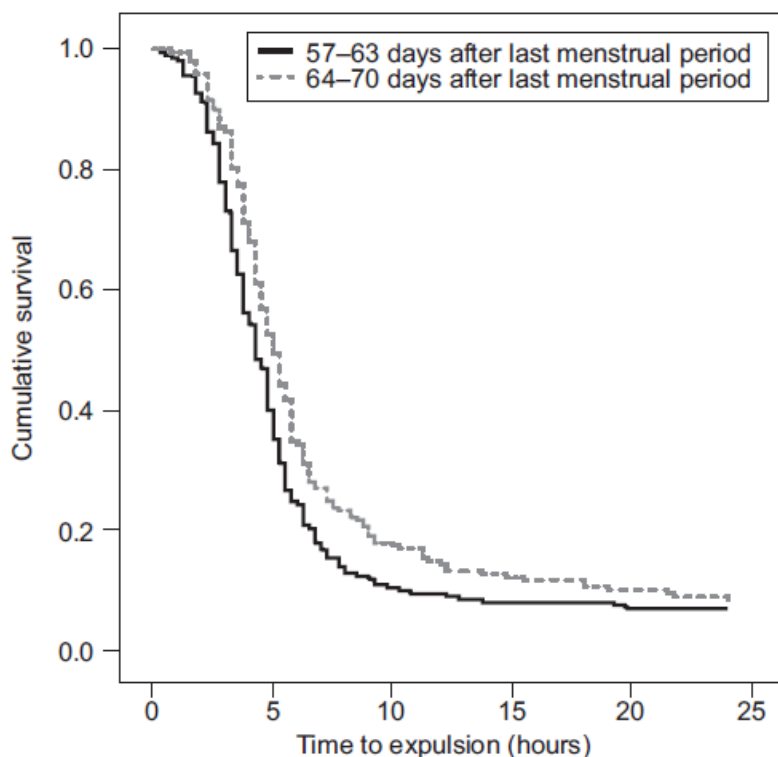
For the majority of women, the most significant cramping and bleeding will occur within 2-24 hours after taking misoprostol. Requiring women to take misoprostol in the office necessitates another visit and can interfere with the woman's ability to make reasonable plans for the expected bleeding and cramping. With the option to take misoprostol at home the woman can:

- **Plan to experience cramping and bleeding at a safe and convenient time when support is available**
- **Minimize loss of income (for childcare or missed days of work)**
- **Experience improved comfort, satisfaction and privacy**

Data (graph below) from Winikoff (2012)¹⁹ shows the time in hours to complete expulsion of the pregnancy after misoprostol administration for gestations at 57-63 and 64-70 days. Within about 5 hours after misoprostol dosing, 50-60% of the MABs are complete.

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Many studies have recorded data on home use in the US and elsewhere and “demonstrated that 87-97% of women find home use of misoprostol acceptable. Home use of misoprostol is now standard in the US.”⁵⁰ The 2009-10 Swica comparative study focused on the option to take both mifepristone and misoprostol at home after being counseled at the office/clinic. There was no significant difference in either efficacy or safety for the 139 women (46%) who took both medications at home compared to 161 women who took mifepristone in the office and misoprostol at home.

Table 8 that follows is a list of studies where data are available on home use of misoprostol and the specific efficacy findings.

⁵⁰ Swica Y, et al. Acceptability of home use of mifepristone for medical abortion. *Contraception* 2013;88:122-127.

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Table 8: Misoprostol Self-administration at Home

Study	Evaluable N	Misoprostol at home	Success	Comment
US Studies				
Gatter 2015 ¹³ US	13,373	All subjects at 24-48 hr	97.7%	Through 63 days; buccal miso 800 mcg
Winikoff 2008 ²³ US	421	All subjects at 24-36 hr	96.2%	Through 63 days; buccal miso 800 mcg
Winikoff 2012 ¹⁹ US	629	All subjects at 24-48 hr	93.5% (Wk 9) 92.8% (Wk 10)	Week 9 v Week 10; buccal miso 800 mcg
Swica 2013 ⁵⁰ US	301	All subjects at 6-48 hr	96.7 %- home mife 95.6%- clinic mife	Through 63 days; 800 mcg miso
Foreign Studies				
Louie 2014 ¹⁴ Azerbaijan	863	794 (92%) at home at 24-48 hr	97%	Through 63 days; buccal miso 800 mcg
Pena 2014 ⁴⁴ Mexico	1,000	All subjects at 24-48 hr	97.3%	Through 63 days; buccal miso 800 mcg
Bracken 2014 ⁴⁹ 4 countries	703 (382 v 321)	543 (77%) took miso at 24-48 hr	94.8% (Wk 9) v 91.9% (Wk 10)	Week* 9 v Week 10 400 mcg sublingual miso used
Boersma 2011 ²² Curacao	307	All subjects at 24-36 hr	97.7%	Through 70 days (Wk 10); GP care ; buccal miso 800 mcg;
Chong 2012 ⁴⁰ 400 v 800 buccal	1115 (559 v 563 were enrolled)	851 (76%) at 36-48 hr	96.8% with <u>home</u> miso; 95.1% with clinic miso	Through 63 days; *DB, RCT in Vietnam and Georgia
Goldstone 2012 ²⁰ Australia:	11,155	All subjects at 24-48 hr	96.5%	Through 63 days; buccal miso 800 mcg
Sanhueza 2015 ⁴⁸	896	All subjects at 24-48 hr	93.3	Through 70 days (Wk 10)
TOTAL	30,763	30,210 (98.2%)	92%-97.7%	Different gestations, and regimens

*DB, RCT: double-blind, randomized clinical trial.

Source: FDA clinical reviewer table.

Reviewer comments:

The above table with data for home administration of misoprostol for 30,763 women in the US and other countries shows a success rate ranging from 91.9 to

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97.7%. The two largest studies (Gatter and Goldstone) pooled showed 97% success using the new proposed dosing regimen with home use of buccal misoprostol. The lowest success rate above of 91.9% in the Bracken study is still supportive for approval and does not differ significantly from results with misoprostol taken in the clinic/office.

Of note is that 4 of the above studies provided data on home use of misoprostol through 70 days gestation.

Home use of misoprostol has been evaluated as part of the proposed protocol in studies including well over 30,000 patients, as well as in studies of home use of both mifepristone and misoprostol. The Raymond (2013) review¹⁸ of early MAB with mifepristone 200 mg and misoprostol (different doses and routes of administration), analyzed 87 trials with 47,283 treated women up to 63 days gestation. The article concludes: “We found no evidence that allowing women to take the misoprostol at home increased the rate of abortion failure or serious complications.” It is also notable that the NAF and ACOG guidances encourage home administration of misoprostol and it has been standard protocol for most PPFA clinics for since 2005.

While we do not have age-specific efficacy data for adolescents who took misoprostol at home, it is evident that many adolescents did take buccal misoprostol at home. In the Goldstone 2012 study, there were eight 14 year olds and 931 women ages 15-19 who took misoprostol at home. In the Gatter 2015 study, there were 24 adolescents age 11-14, 82 age 15, 216 age 16, and 435 age 17 who took misoprostol at home. The overall efficacy in these two large studies was excellent, as previously noted.

Reviewer’s Final Recommendation:

There is no medical rationale against permitting the woman to be given the misoprostol on the day of the initial clinic/office visit and self-administer it at a convenient time in the next 24-48 hours at home. This would avoid another visit and the time, transportation, loss of work, inconvenience, etc. that such a visit would involve. Furthermore, given the fact that 22-38% of women abort within 3 hours and 50-60% within 5 hours of buccal misoprostol¹⁹, it is preferable for the woman to be in a convenient, safe place (home or at a support person’s location) for the expected uterine cramping and vaginal bleeding to occur. The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol shows acceptable efficacy when misoprostol is self-administered at home.

6.1.9 Use of a Repeat Dose of Misoprostol if Needed

Several studies using buccal misoprostol allowed the option of repeat misoprostol at follow-up one week after mifepristone for persistent gestational sac; however, only a few

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studies report specific outcomes. The Chen and Creinin 2015 review¹² of mifepristone with buccal misoprostol for MAB reported on four studies. Chong (2012)⁴⁰ provided additional information from 1,122 women. In the study protocols, women with an ongoing pregnancy at follow-up were recommended to undergo uterine suction curettage, whereas women who had retained products of conception were given the options of expectant management, suction curettage/aspiration, or a second dose of misoprostol. Limited additional data were provided by Gatter (2015)¹³: data on the use of a repeat dose of misoprostol were available from a subset of 7,335 women, of whom 87 (1.2%) received a repeat dose. Efficacy results, however, are not stated in the Gatter article, so this study is not included in Table 9, which highlights success rates after a repeat dose of misoprostol in seven published articles that included this specific outcome.

Table 9: Success with a Repeat Dose of Misoprostol - Incomplete MAB

Study/Country	Total N	Mife-Miso Interval (hrs)	Took 2 nd Dose	Success with 2 nd dose N (%)	Comment
*Raghavan 2010 ⁵¹ Moldova	277	24	2	2 (100)	Buccal Miso 400
*Winikoff 2008 ²³ US	421	24-36	14	13 (93)	Buccal Miso 800
*Winikoff 2012 ¹⁹ US	629	24-48	^Y 20	^Y Wk 9- 11 (91) Wk 10: 9 (67)	Week 9 v. Week 10: Buccal Miso 800
*Louie 2014 ¹⁴ Azerbaijan	863	24-48	16	16 (100)	Buccal Miso 800
Chong 2012 ⁴⁰ Georgia, Vietnam	1122	36-48	47	43 (92)	Buccal Miso 400 and 800 mcg
Boersma 2011 ²² Curacao	307	24-36 hr	5	4 (80)	GP care; Buccal Miso 800 at home
Bracken 2014 ⁴⁹ 4 countries	703	24-48 hr	33	29 (88)	Sublingual Miso 400
TOTALS	4,018	--	137 (3.4%)	123 (90%)	

*These 4 studies are in Table 4 of the Chen and Creinin 2015 review article.

^YThese data are directly from the Winikoff article; the Chen and Creinin review had incorrect data.
 Source: table modified by FDA reviewer from Chen and Creinin 2015 article and 3 other studies.

⁵¹ Raghavan S, et al. Comparison of 400 mcg buccal and 400 mcg sublingual misoprostol after mifepristone medical abortion through 63 days' LMP: a randomized controlled trial. Contraception 2010; 82:513-9.

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Reviewer's comment:

The completion success rates shown above are high. While only 3.4% of the women took a second misoprostol dose, 90% of these women avoided a surgical procedure to complete their termination. We believe the option of a repeat dose of misoprostol is acceptable and safe in the case that complete expulsion has not occurred after initial dosing (provided that the pregnancy is not still ongoing): it offers a choice for the healthcare provider and the patient on how to manage an incomplete expulsion (retained products of conception) following the initial treatment. As noted above, the other options are expectant management, suction aspiration in the office, or a surgical D&C in the operating room. It is also of note that it is standard protocol in many US clinics to offer the choice of a repeat misoprostol dose, especially for women with an incomplete termination (retained tissue/clots or a documented non-viable pregnancy). A second dose of misoprostol is generally not offered in the case of a documented ongoing pregnancy following use of mifepristone and misoprostol.

Reviewer's Final Recommendation:

Use of a repeat dose of misoprostol may be offered when using the new dosing regimen if the pregnancy has ended, but the expulsion is incomplete.

6.1.10 Physician v Other Healthcare Provider Treatment

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies took place in varying settings (urban, rural, international, low resource). The efficacy results are as follows:

- Olavarietta⁸⁵ demonstrated efficacy of 97.9% when the MAB was provided by nurses as compared with 98.4% with physicians
- Kopp Kallner⁸⁴ showed efficacy of 99% with certified nurse midwives versus 97.4% with physicians
- Warriner⁵² demonstrated efficacy of 97.4% with nurses versus 96.3% with physicians
- Puri⁸³ showed efficacy of 96.8% compared with 97.4% in the "standard care" group

Reviewer comment:

The above findings for MAB efficacy from 5 studies clearly demonstrates that efficacy is the same with non-physician providers compared to physicians or the

⁵² Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61.

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“standard care” treatment.

6.1.11 Follow-up Timing and Method

Concerning follow-up timing and method, follow-up within the 7-14 day interval after mifepristone administration is universally recommended; however, follow-up does not necessarily need to be done as currently labeled “in the clinic or healthcare provider’s office 14 days after Mifeprex administration.”

One strong argument for flexibility in follow-up timing, location and method after the administration of Mifeprex and misoprostol is to avoid placing an undue burden on either the provider or the patient, while maintaining the ability to identify incomplete terminations. The currently approved labeling specifies three visits (two for dosing, one for follow-up) at fairly rigid times that are often not practical, convenient or necessary.

Several articles were submitted by the Applicant to support flexible follow-up. The most noteworthy article is the 2013 Raymond review¹⁸ of over 45,000 MABs using 200 mg oral mifepristone that concluded: “we observed no significant association between abortion failure rates and the timing of the follow-up evaluation.” This topic is discussed thoroughly in the Section Submission-Specific Primary Safety Concerns.

Reviewer comment:

Follow-up during the 7-14 day window after the administration of mifepristone is necessary to determine that the termination was successful and the woman is in good health. If for some reason the follow-up contact is not made (the woman is “lost to follow-up”), the clinical guidelines of NAF state that “all attempts to contact the patient (phone calls and letters) must be documented in the patient’s medical record.” This guideline emphasizes the importance of follow-up but accepts the fact that women are sometimes lost to follow-up and there is no mechanism that can guarantee 100% follow-up in the normal clinical setting.

Reviewer’s Final Recommendation:

Follow-up after taking Mifeprex and misoprostol is necessary. The exact timing and method should be flexible and determined jointly by the healthcare provider and the individual woman being treated, and should follow the standard guidelines for the office/clinic where the Mifeprex is being dispensed. Fortunately, there are several choices/methods of follow-up that can be used and it appears that no single option is superior to the others. The woman should always have the option to be seen at the office/clinic.

6.1.12 Subpopulations

Parity

The Raymond (2013) review article¹⁸ had 74 trials with parity data for ~ 32,000 women. In 34 trials whose study populations comprised > 50% nulliparous women, the MAB success rate was 96.4%; in 40 trials with ≤ 50% nulliparous women, the success rate was 94.9%. This suggests that women who have not had a previous term pregnancy

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delivery have a slightly higher early MAB success rate. These data are not definitive, however, because such factors as the dosing regimen, route of administration, and gestational age could also influence the success rates.

Previous abortion

One study²⁶ found that success rates are slightly better in women who have not had a previous abortion. Prior abortion, however, did not appear to be an important risk factor for abortion failure or success (Raymond¹⁸).

Race

There does not appear to be any efficacy difference based on race. Results are reported in studies enrolling a large number of women. Gatter (2015)¹³ had five racial/ethnicity groups among over 13,000 women at the PPFA centers in the Los Angeles area; the success rates ranged from a low of 97.2% (African-American) to a high of 97.8% (White, Asian and Other), which is not clinically or statistically significant.

Adolescents v. Older Women

There are at least three articles that support the efficacy of MAB in adolescents; each study used the same definition of success as the need for no further medical or surgical intervention:

- Phelps et al. 2001⁵³ conducted a pilot study in 28 adolescents aged 14-17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. All 28 had complete medical terminations without complications or surgical intervention. Five adolescents did not require any misoprostol.
- Niinimaki et al. April 2011:⁵⁴ Finnish Registry from 2000-06 comparing rates of AEs in adolescents and adult women with MAB at ≤ 20 weeks gestation, which included 3,024 women < age 18 and 24,006 women age 18 or older. By gestational age, 2,424 adolescents were < 64 days gestation and 139 were within 64-84 days gestation. The specific dose regimens are not stated and may have varied according to the gestational ages. The odds ratio for an incomplete abortion for adolescents under age 18 compared to the women ≥ age 18 was 0.69, meaning that the younger women had a lower rate of incomplete abortions.
- Gatter, Cleland and Nucatola (2015):¹³ US data using the proposed regimen of mifepristone 200 mg and misoprostol 800 mcg buccally through 63 days included 283 women aged 17 years and 322 under age 17 (see Table 10). The 605 women under age 18 had a 98.7% success rate while the 6,674 18-24 year olds had a 98.1% success rate. The four older age groups had success rates that ranged from 96.5 to 97.5% without any need for a surgical procedure and additional treatment. In

⁵³ Phelps RH, et al. Mifepristone abortion in minors. *Contraception* 2001;64:339-343.

⁵⁴ Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. *BJM* 2011;342: d2111.

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the pediatric population, there were no cases requiring transfusion, hospitalization or treatment for severe infection.

The table below shows the age distribution from the Gatter study. There were 24 adolescents between ages 11-14, 82 adolescents age 15, and 216 age 16 totaling 322 adolescents. As noted, 283 adolescents were age 17.

Table 10: MAB Success by Age Group

Age Group (years)	Total N Success (%)	Comment
< 18	605 (98.7)	322 were age 11-16 283 were age 17
18-24	6684 (98.1)	The age distribution here is representative of other US data on MAB - largest group is age 18-24 followed by age 25-29
25-29	3317 (97.5)	
30-34	1613 (96.5)	
35-39	855 (97.0)	
40+	299 (97.3)	
TOTAL	13,373 97.7% overall success	

Source: Data from Gatter 2015 review.

Reviewer comments:

Data from 3,657 adolescents under age 18 in the above three studies shows a MAB success rate that is consistently equal to or higher than that found in the women older than age 17. It is interesting that five (18%) of the adolescents in the Phelps study did not even need misoprostol. The percentage of women not needing any misoprostol is generally much lower, perhaps 1-3%, in other early MAB studies. From the articles reviewed, efficacy of early MAB in the adolescent population is not a concern.

Additional adolescent data were reported in the Goldstone 2012 study²⁰, where there were eight 14 year olds and 931 women ages 15-19 who took misoprostol at home for a MAB up to 63 days gestation. Efficacy and safety data by age groups were not reported in the article.

6.1.13 Analysis of Clinical Information Relevant to Dosing Recommendations

As noted in some of the reviewer comments and tables, there is evidence that lower doses of misoprostol (400 mcg), other ROAs (vaginal and sublingual), inclusion of more advanced gestational ages, and different dosing intervals between mifepristone and misoprostol have shown acceptable efficacy and safety results. However, for the purposes of this NDA review, our final recommendations are focused on the dosing regimen and other requests specifically made by the Applicant.

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6.1.14 Discussion of Persistence of Efficacy and/or Tolerance Effects

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

6.1.15 Additional Efficacy Issues/Analyses

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

Reviewer Final Recommendation:

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

7 Review of Safety

Safety Summary

- Medical abortion with the new proposed regimen of Mifeprex 200 mg followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation is safe. Major adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are reported rarely in the literature on over 30,000 patients. The rates, when noted, are exceedingly rare, generally far below 0.1% for any individual adverse event. The number of postmarketing deaths associated with Mifeprex pharmacovigilance is very low. Non-vaginal routes of administration of misoprostol have increased and since the *C. sordellii* deaths associated with vaginal misoprostol, there have been no *C. sordellii* deaths. Given that the numbers of these adverse events appear to be stable or decreased over time, it is likely that these serious adverse events will remain acceptably low.
- Common adverse events associated with medical abortion occur at varying but acceptable rates.
- There are scarce cases of uterine rupture associated with early medical abortion. Medical abortion using mifepristone with or without misoprostol in the first trimester is safe from this perspective.

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- There does appear to be an association between angioedema and mifepristone administration. The risks of anaphylaxis and angioedema should be included in the labeling for Mifeprex and there should be continued pharmacovigilance for anaphylaxis.
- Home use of misoprostol has been evaluated as part of the proposed dosing regimen in studies including well over 30,000 patients, demonstrating an acceptable safety profile, with rates of adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol. Home use of misoprostol can increase patient convenience, autonomy and privacy without increased burden on the healthcare system.
- In the articles about repeat misoprostol after mifepristone administration, there is little information provided about safety. The need for a second dose is a relatively uncommon occurrence. In studies of medical abortion using misoprostol alone, using two or more doses as compared to one dose of misoprostol does increase the risk of the common adverse event of diarrhea. There are a very few reports of uterine rupture with multiple doses of misoprostol, in almost all cases in women with prior uterine surgery, such as a cesarean section.
- The Applicant demonstrates that alternatives to in-clinic follow-up, including standardized questions, telephone follow-up, and use of low and high sensitivity urine pregnancy tests, serum pregnancy tests, and ultrasound are effective and safe. Loss-to-follow-up rates do not exceed those of in-clinic follow-up. This option can increase flexibility and accessibility of medical abortion for women.
- Medical abortion in adolescents appears to be at least as safe, if not safer, as in adult women. These data support the safety of Mifeprex in adolescents and satisfy requirements for PREA. No information on safety or efficacy if used in premenarchal girls is required, as the medication is not indicated in that subset of the pediatric population.
- Midlevel providers in the United States, such as nurse practitioners, nurse midwives and physician assistants currently provide family planning services and abortion care, including medical abortion care, under the supervision of physicians. In light of the REMS requirements, midlevel providers who are currently practicing abortion care are doing so under the supervision of physicians. Therefore, facilities that employ midlevel providers already have an infrastructure in place for consultation and referral if, as required under the REMS, a prescriber is unable to provide additional care, including surgical management if needed.
- It is appropriate to modify the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." FDA has received

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such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely. For this reason, FDA does not believe ongoing reporting of all of the specified adverse events is warranted. The proposed Prescriber's Agreement Form (to replace the Prescriber's Agreement) will continue to require that qualified healthcare providers report any deaths. The Applicant will still be required by law, as is every NDA holder, 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.

- Upon review of historical documents and of current guidelines for REMS materials, the phrase "under Federal law" can be removed from the Prescribers' Agreement. We concur with (b) (6) review of the REMS document.
- The revised Indication Statement should read:

"Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation." Safe use of Mifeprex would be enhanced when other information necessary to describe appropriate use (i.e., the need to use Mifeprex in a combined regimen with misoprostol and the gestational age for use) is included in the Indication Statement. This would be consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include "Information if drug is to be used only in conjunction with another therapy."

7.1 Methods

The assessment of the clinical safety of Mifeprex through 70 days gestation is based on the Applicant's submission of numerous articles from the peer-reviewed medical literature. The various studies have different designs, inclusion criteria, dosing regimens and endpoints for safety and efficacy. For the evaluation of safety, this reviewer focused on the studies that evaluated the proposed dosing regimen. All the articles used for this review can be found in the extensive list of references in Section 9.6 at the end of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The reviewer evaluated safety based on the studies that focused on the proposed dosing regimen, specifically Mifeprex 200 mg followed by misoprostol 800 mcg buccally 24-48 hours later, as listed in Table 11 below. Supportive data from studies that have less specific numerical data or studies that included other regimens, specifically with different routes of administration of misoprostol (vaginal, oral, sublingual) are not included in this portion of the review, but are discussed in Sections Major Safety Results and Supportive Safety Results. Table 11 lists the studies referenced in these discussions.

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Table 11: Studies Used to Evaluate Safety

Study	
USA	International
Gatter 2015 ¹³ , retrospective	Ngoc 2014 ¹⁶ , Vietnam, prospective
Ireland 2015 ¹⁵ , retrospective	Goldstone 2012 ²⁰ , Australia, retrospective
Chong 2015 ¹⁷ , prospective single-arm	Boersma 2011 ²² , Curacao, prospective
Winikoff 2012 ¹⁹ , prospective	
Grossman 2011 ³⁶ , prospective	
Winikoff 2008 ²³ , prospective RCT	
Creinin 2007 ²⁵ , prospective	
Middleton 2005 ²⁴ , prospective	

Source: NDA clinical reviewer table.

7.1.2 Categorization of Adverse Events

For the purposes of this review, adverse events categorized as serious include death; hospitalization; infection, including severe infection requiring hospitalization; bleeding requiring transfusion; and ectopic pregnancy. Other non-serious adverse events include: nausea, vomiting, diarrhea, fever, bleeding and cramping.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data are not pooled across studies as the study designs are quite different. The incidence of individual adverse events is noted for each study, and can be used to provide an estimated range.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Per the Applicant, there have been approximately 2.5 million US uses of Mifeprex by US women since its approval in 2000. If evaluation is limited to the studies listed in Table 11 focusing specifically on the proposed new dosing regimen, exposure for this safety analysis is based on well over 30,000 patients. The exact number cannot be determined because two retrospective studies (Gatter¹³ and Ireland¹⁵) are likely based on overlapping cohorts of patients from Planned Parenthood clinics in Los Angeles. There are likely some differences in the demographic data for the different studies; therefore, the descriptions are separated into US and international data. However, it is doubtful

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that demographic differences such as race or ethnicity are clinically meaningful in relation to the safety and efficacy of medical abortion. The data do include adolescents exposed to Mifeprex; information on safety in this population is discussed in Section 7.4.5.

7.2.2 Explorations for Dose Response

NA for this review.

7.2.3 Special Animal and/or In Vitro Testing

NA for this review.

7.2.4 Routine Clinical Testing

From this reviewer's assessment of the literature, no routine clinical testing is needed to evaluate the proposed changes to the Mifeprex labeling.

7.2.5 Metabolic, Clearance, and Interaction Workup

NA for this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please see Important Safety Issues with Consideration to Related Drugs for discussion of potential adverse events for drugs in this class.

7.3 Major Safety Results

7.3.1 Deaths

Deaths are rare with medical abortion. Most of the articles provided did not specifically report on deaths with medical abortion. Among the seven US studies, only one reported on deaths (Grossman, 2011³⁶) and noted zero deaths among 578 subjects. Among the three international studies, only one²⁰ reported on deaths. In this retrospective review of 13,345 medical abortions with the proposed regimen, the authors reported only one death, yielding a rate of 0.007%. More information on deaths associated with medical abortion is found in Section 8 Postmarket Experience.

7.3.2 Nonfatal Serious Adverse Events

The nonfatal serious adverse events typically discussed in the literature are hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. See narratives below and Table 12, Table 13, and Table 14 for details.

Hospitalization data:

Most articles do not report hospitalization data. In the US studies, 19 patients were reported as being hospitalized out of a total of 16,696 subjects. The overall rates range

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from 0.003-1.1%. Only three articles separated out hospitalizations by gestational age. In Gatter 2015¹³, there were 3/8495 hospitalizations among women \leq 49 days, 3/3142 among women at 50-56 days gestation and none among women at 57-63 days. In Winikoff 2012¹⁹, there were only two hospitalizations, both among women at 57-63 days, and none in the 64-70 days gestation group. In Creinin²⁵ two of six total hospitalizations were in the 50-56 days group and two in the 57-63 days group. The two remaining hospitalizations in that study were unrelated to study drug and gestational age information was not provided for these two cases. There were none among women at 64-70 days gestation. See Table 12 below.

Among the international studies, only 3 of 15,109 women were hospitalized, with rates from 0.07-0.6%. These rates were not separated out by gestational age. See Table 12.

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Study	Design	Subjects (N)	Hospitalizations by gestational age [Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015 ¹³	retrospective	13,373	6‡ (0.04%)	N=8945 3/8945 (0.03%)	N=3142 (0.1%)	N=1286 0	N/A
Chong 2015 ¹⁷	prospective	400	2 (0.5%)	NR*	NR	NR	N/A
Winikoff 2012 ¹⁹	prospective	729	2 (0.27%)	N/A	N/A	N=325 2 (0.61%) [^]	N=304 0%
Grossman 2011 ³⁶	prospective	578	0	N=283 0%	N=103 0%	N=63 0%	N/A
Winikoff 2008 ²³	prospective	421	3(0.71%)	N=213 NR	N=93 NR	N= 115 NR	N/A
Creinin 2007 ²⁵	prospective	546	6 (1.1%)§	N=229 0%	N=172 2 (1.16%)§	N=145 2 (1.38%)§	NA
Middleton 2005 ²⁴	prospective	223	NR	NR	NR	N/A	N/A
International							
Ngoc 2014 ¹⁶ Vietnam	prospective	1433	1 (0.07%)	NR	NR	NR	N/A
Goldstone 2012 ²⁰ Australia	retrospective	13,345	NR	N=11,855 NR	N= 1441 NR	N=49 NR	N/A
Boersma 2011 ²² Curacao	prospective	331	2/331 (0.6%)	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

* NR= not reported

‡numbers of hospitalizations for Gatter study includes those for bleeding and infection in subsequent tables.

[^] includes woman with sepsis noted in Table 13, and one woman with chronic pancreatitis, recurrent.

§includes subjects receiving transfusions noted in Table 14.

Source: NDA clinical reviewer table.Serious infection:

Infections requiring hospitalization or IV antibiotics were rare in the studies. Only three US studies captured this information, with rates ranging from 0-0.015%. Two studies separated this information out by gestational age. In Gatter 2015¹³, the two serious infections were in women ≤ 49 days gestation. There were no serious infections in

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women at 50-56 or 57-63 days gestation. In Winikoff 2012¹⁹, there was one serious infection in a woman at 57-63 days and none in women at 64-70 days. See Table 13.

Among the international studies, there were five women hospitalized with rates from 0.03-0.07%. This information was not broken down by gestational age. See Table 13.

Table 13: Serious Infection by Gestational Age

Study	Design	Subjects (N)	Serious Infection by gestational age (Total N in subgroup, rate [%])				
			All Gestational Ages (Overall/ not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015 ¹³	retrospective	13,373	2 (0.015%)	N= 8945 2 (0.022%)	N= 3142 0%	N=1286 0%	N/A
Chong 2015 ¹⁷	prospective	400	NR*	NR	NR	NR	N/A
Winikoff 2012 ¹⁹	prospective	729	1 (0.014%)	N/A	N/A	N=325 1 (0.31%)	N=304 0%
Grossman 2011 ³⁶	prospective	578	NR	N=283 NR	N=103 NR	N=63 NR	N/A
Winikoff 2008 ²³	prospective	421	NR	N=213 NR	N=93 NR	N=115 NR	N/A
Creinin 2007 ²⁵	prospective	546	0	N=229 0%	N=172 0%	N=145 0%	N/A
Middleton 2005 ²⁴	prospective	223	NR	NR	NR	N/A	N/A
International							
Ngoc 2014 ¹⁶ Vietnam	prospective	1433	1 (0.07%)	NR	NR	NR	N/A
Goldstone 2012 ²⁰ Australia	retrospective	13,345	4 (0.03%)	N=11,855 NR	N=1441 NR	N=49 NR	N/A
Boersma 2011 ²² Curacao	prospective	331	NR	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

* NR= not reported

Source: NDA clinical reviewer table.

Transfusion data:

With regard to bleeding requiring transfusion, five of the seven US studies included this information as shown in Table 14. The rates of transfusion range from 0.03-0.7%.

Three of the studies provided a breakdown by gestational age. In Gatter 2015¹³, there were the following: one woman in the ≤ 49 days group, three in the 50-56 days and zero in the 57-63 days group. In Winikoff 2012¹⁹, there were: two in the 57-63 days group

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and 1 in the 64-70 days group. In Creinin 2007²⁵, there were two women transfused each in the 50-56 days and 57-63 days. Only one international study²⁰ (Goldstone 2012) reported on transfusions and 11/13,345 women or 0.08% required transfusion.

Table 14: Transfusion by Gestational Age

Study	Design	Subjects (N)	Bleeding Requiring Blood Transfusion by gestational age [Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015¹³	retrospective	13,373	4 (0.03%)	N=8945 1 (0.01%)	N=3142 3 (0.1%)	N=1286 0	N/A
Chong 2015¹⁷	prospective	400	NR	NR	NR	NR	N/A
Winikoff 2012¹⁹	prospective	729	3 (0.41%)	N/A	N/A	N=325 2 (0.53%)	N=304 1 (0.29%)
Grossman 2011³⁶	prospective	578	1 (0.17%)	N=283 NR	N=103 NR	N=63 NR	N/A
Winikoff 2008²³	prospective	421	NR	N=213 NR	N=93 NR	N=115 NR	N/A
Creinin 2007²⁵	prospective	546	4(0.7%)	N=229 0	N=172 2 (0.36%)	N=145 2 (0.36%)	N/A
Middleton 2005²⁴	prospective	223	1 (0.45%)	NR	NR	N/A	N/A
International							
Ngoc 2014¹⁶ Vietnam	prospective	1433	NR	NR	NR	NR	N/A
Goldstone 2012²⁰ Australia	retrospective	13,345	11 (0.08%)	N=11,855 NR	N=1441 NR	N=49 NR	N/A
Boersma 2011²² Curacao	prospective	331	NR	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

*NR= not reported

Source: NDA clinical reviewer table.

Ectopic pregnancy:

Ectopic pregnancies were rarely reported in the supporting literature submitted with this efficacy supplement. Only one ectopic pregnancy was reported among 847 patients (0.12%) in Winikoff 2008²³.

Several studies also included less detailed, though still useful, information on adverse events. Ireland et al¹⁵ conducted a retrospective review of 30,146 women undergoing

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medical or surgical abortion at ≤ 63 days gestation at Planned Parenthood clinics in Los Angeles between November 1, 2010 and August 31, 2013. The authors reported that 29 women of 13,221 (0.1%) undergoing medical abortion experienced a major complication, which was defined as including: emergency department presentation, hospitalization, infection, perforation and hemorrhage requiring transfusion. The article did not specify the rate of each event. No deaths or ectopic pregnancies were reported in this study. In 2011, Grossman³⁶ reported on a study of medical abortion provided through telemedicine, in which 578 women seeking abortion services at Planned Parenthood of the Heartland clinics in Iowa were offered in-person services or telemedicine services. The serious adverse event outcomes are reported in Table 12, Table 13 and Table 14 above, but in addition, he reported on adverse events among all medical abortion patients from July 1, 2008 through October 31, 2009 (a wider time frame than the study itself). Four of 1,172 telemedicine patients (0.3%) required a blood transfusion compared to 0.1% of 2,384 in-person patients. These figures were reported in the paper to support study findings of low rates of serious adverse events, including transfusion. Pena (2014)⁴⁴ reported on 1,000 women in Mexico who had a medical abortion up to 63 days gestation. Their paper reported that “there were no serious complications as defined by any occurrence that was unexpected, serious, and related to the induced abortion.” Upadhyay et al⁵⁵ used 2009 through 2010 patient-level billing data from Medi-Cal, California’s state Medicaid program, to evaluate the incidence of complications after abortion, including medical abortion. Major complications were defined as those which required hospitalization, surgery or blood transfusion. There were 11,319 medical abortions, with 35 women (0.31%) having a major complication.

Winikoff (2012)¹⁹ provides data on other serious adverse events through 70 days. Regarding hospitalization, there were zero hospitalizations among 350 women receiving medical abortion at 64-70 days compared with 2/379 women at 57-63 days (0.5% rate). There were no serious infections in the 64-70 day group, compared with 1/379 (0.3% rate) in the 57-63 day group. There was one transfusion (1/350=0.3% rate) in the 64-70 day group, compared with 2/379 (0.5% rate) in the 57-63 day group.

Reviewer comments:

(b) (4)
. Serious adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are rarely reported in the literature. The rates, when noted are exceedingly rare, with rates generally far below 1.0% for any individual adverse event. This indicates that medical abortion with the proposed regimen up through 63 days is safe.

⁵⁵ Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. *Obstet Gynecol* 2015;125(1):175-183.

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Serious fatal or nonfatal adverse events in the 64-70 days gestation group, were evaluated in one US study (Winikoff 2012)¹⁹. This study with 379 women in the 64-70 day range is reassuring in that the rates of hospitalization, serious infection and transfusion are no higher than in the lower gestational age ranges. Based on the available safety data on medical abortion in totality, it appears that serious fatal or nonfatal adverse events are very rare through 70 days as well. This regimen should be approved for use through 70 days gestation.

Reviewer's Final Recommendation:

The regimen of mifepristone 200 mg followed by misoprostol 800 mcg buccally in 24-48 hours is safe to approve for use through 70 days gestation.

7.3.3 Dropouts and/or Discontinuations

The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc 2014¹⁶) to 22% in the Grossman³⁶ study using telemedicine to deliver medical abortion services. One study noted no differences in demographics between the subjects on whom follow-up was available, compared with those on whom no follow-up information was available. Only two studies evaluated other subgroups of women lost to follow-up. Gatter et al 2015¹³ found a higher odds of loss to follow-up with age <18 and with income at or below the federal poverty level. Additionally they noted increased odds of loss to follow-up with increasing gestational age. As compared with women 43-49 days gestation, the Odds Ratio (OR) for loss to follow-up at 50-56 days was 1.17 (95% CI 1.05-1.31) and at 57-63 days was 1.28 (95% CI 1.10-1.48). The Boersma study²² had a 7% loss to follow-up rate. The rate of loss to follow-up was 6.5% at ≤ 49 days, 7.6% at 50-63 days and 7.7% at 64-70 days. No tests for significance were applied to these numbers. Only one study reported on withdrawals: Winikoff 2012¹⁹ reported that 0.27% of patients withdrew and noted this was similar to rates previously reported in the literature.

Reviewer comment:

There is a wide range of loss to follow-up in the studies submitted with the efficacy supplement. The loss to follow-up rate cannot be reliably linked to method of follow-up, though it is notable that the lowest rate of loss-to-follow-up occurred in the Ngoc trial with telephone follow-up (0.6%) and the highest with abortion services provided via telemedicine (22%). The range of loss to follow-up is well-within the range documented in literature covering real-world abortion practice.¹

7.4 Significant Adverse Events

The label for misoprostol currently includes a boxed warning against the use past 8 weeks gestation, due to the risk of uterine rupture. The (b) (6) safety reviewer and

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(b) (6) conducted separate literature searches on this topic. Chen et al 2008⁵⁶ evaluated 488 women with a mean gestational age of 7.8 weeks who received 800 mcg misoprostol as part of a randomized study of misoprostol vs. curettage for early pregnancy failure. They found that 78 (16%) of women in the misoprostol group had previous uterine surgery (>1 C-section or myomectomy). There were no uterine ruptures in that study. Gautam et al⁵⁷ reported in 2003 on 66 women up to 60 days' gestation and with previous Caesarean section scar, who received misoprostol 800 mcg for termination and found no uterine ruptures. The literature search also revealed five case reports of uterine rupture.^{58, 59, 60, 61, 62} Of these five cases, three occurred with combined mifepristone/misoprostol dosing. Four women had uterine scars, most commonly from at least one prior cesarean section, and one of them had had a prior uterine rupture in labor. Only one woman had no prior uterine scar (Willmott). In these case reports and studies, women received varying doses of misoprostol ranging from 400 mcg to 600 mcg to 800 mcg, and in two, the women received multiple doses of misoprostol (4 and 5 doses in the Wilmot and Bika reports respectively). The women required surgery to repair the uterus or hysterectomy and transfusion. See Table 15.

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⁵⁶ Chen BA, Reeves MF, Creinin MD, Gilles JM, Barnhart K, Westhoff C, Zhang J. National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial. *Am J Obstet Gynecol* 2008;198(6):626. d1-5 doi: 10.1016/j.ajog.2007.11.045. Epub Feb 15, 2008.

⁵⁷ Gautam R, Agrawal V. Early medical termination pregnancy with methotrexate and misoprostol in lower segment cesarean section cases. *J Obstet Gynaecol Res* 2003; 29(4):251-256.

⁵⁸ Khan S, et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. *J Obstet Gynaecol* 2007;27(8):869-870.

⁵⁹ Kim JO, et al. Oral misoprostol and uterine rupture in the first trimester of pregnancy: A case report. *Reproductive Toxicology* 2005;20:575-577.

⁶⁰ Jwarah E, Greenhalf JO. Rupture of the uterus after 800 micrograms misoprostol given vaginally for termination of pregnancy. *BJOG* 2000;107:807.

⁶¹ Bika O, Huned D, Jha S, Selby K. Uterine rupture following termination of pregnancy in a scarred uterus *J Obstet Gynaecol* 2014;34(2):198-9. doi: 10.3109/01443615.2013.841132.

⁶² Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. *BJOG* 2008;115:1575-1577.

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Table 15: Uterine Rupture with Misoprostol Case Reports

Study	GA (weeks)	Mifepristone used?	Dose of Misoprostol	Number of doses of misoprostol	Risk Factor for Rupture
Khan ⁵⁸	8	Yes; dose not specified	600 mcg	1	1 prior C-section, 1 prior uterine rupture at 32 weeks
Kim ⁵⁹	8	No	400 mcg	1	1 prior C-section
Jwarah ⁶⁰	8 2/7	No	800 mcg	1	1 prior C-section
Bika ⁶¹	10 2/7	Yes; 200 mg	800 mcg x 2 doses then 400 mcg x 2 doses	4	2 prior C-sections
Willmott ⁶²	12 3/7	Yes; 200 mg	400 mcg	5	none

Source: NDA clinical reviewer table.

(b) (6) also conducted a review of FAERS cases from January 1, 1965 through October 15, 2015 for reports of uterine rupture with mifepristone alone, misoprostol alone, or a combined regimen, with special interest in cases occurring in women ≤ 10 weeks pregnant (≤ 70 days). The FAERS search retrieved 80 cases of uterine rupture, with 77 citing misoprostol use alone and 3 citing both mifepristone and misoprostol use. No cases of uterine rupture were reported with mifepristone use alone. Vaginal administration of misoprostol was documented in the majority of the cases. The majority of the FAERS cases either occurred in the 3rd trimester of pregnancy, or did not report gestational age. In the cases where the gestational age was not reported, it is likely that most of these cases occurred during the 2nd or 3rd trimester, as many noted the induction of labor as the reason for misoprostol use. The majority of cases also noted at least one additional potential risk factor, with a history of at least one previous c-section, or the use of additional uterotonic drugs (e.g., oxytocin or dinoprostone) being the most commonly reported. The use of misoprostol during the 3rd trimester for the induction of labor, cervical ripening, or both, in women that had at least one previous c-section, was also documented in many cases.

There were only two cases (2.5% of all reports) that reported uterine rupture within the first 10 weeks of pregnancy. In both cases, misoprostol alone was utilized for termination of pregnancy. The first case provided minimal information other than documentation of a 5 week gestation, and an ultrasound noting “an important uterine separation” during an unspecified time after misoprostol (route not specified) administration. The remaining case was also a published case report in which uterine rupture was documented as occurring approximately 2.5 hours after 800 mcg of misoprostol was administered vaginally for cervical preparation prior to surgical termination of pregnancy. The patient was 8 weeks and 2 days pregnant, had a history of a prior c-section, and was of advanced maternal age. (b) (6) concluded that uterine

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rupture associated with the use of mifepristone alone, misoprostol alone, or both, is likely a rare event in the 1st trimester.

Reviewer comment:

Based on the scarcity of reported cases in the first trimester of pregnancy, uterine rupture associated with early medical abortion using mifepristone with or without misoprostol is likely rare. There are a three reports of uterine rupture with mifepristone and misoprostol in the first trimester, most of which occurred in women with prior uterine surgery (e.g., a cesarean section).

7.4.1 Submission-Specific Primary Safety Concerns**Summary of requested dosing changes in the NDA Supplement that could affect safety:****1. Proposing a new dosing regimen that uses mifepristone 200 mg oral and the buccal administration of 800 mcg misoprostol at 24-48 hours after Mifeprex and increasing the gestational age from 49 days to 70 days**

The Applicant submitted several articles in support of the proposed dosing regimen as well as increasing the gestational age through 70 days using the proposed regimen, including the 24-48 hour interval. See Section 7.3 Major Safety Results for fatal and nonfatal serious adverse events reported with the proposed regimen and gestational age. The data submitted show these events to be exceedingly rare, indicating that the new dosing regimen and increasing the gestational age to 70 days is safe. Please see Section 7.3 Major Safety Results on Nonfatal Serious Adverse Events for a review of this information.

In further support of changing the dosing interval for misoprostol to 24-48 hours after mifepristone is taken, the Applicant also provided a systematic review by Shaw et al.⁶³ In this study the authors searched Medline, ClinicalTrials.gov, Popline and the Cochrane Controlled Trials Register and included 20 randomized controlled trials and 9 observational studies. The majority of the studies used the proposed 200 mg dose of mifepristone, but three RCTs and two observational studies used 600 mg of mifepristone. The doses and route of misoprostol administration varied, including doses of 400 mcg, 600 mcg, and 800 mcg, some with repeat doses, and included vaginal, buccal, oral and sublingual routes. There was wide variation in time to administration of the misoprostol, ranging from <24 hours, 24-48 hours, 36-48 hours. Adverse events were not reported consistently. There was no statistically significant difference in nausea, vomiting or diarrhea.

⁶³ Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. *Obstet Gynecol* 2013;121(6):1335-1347.

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Reviewer comment:

Unlike the efficacy data, which is based on studies that look specifically at individual changes proposed by the Applicant, the adverse event data typically come from studies or reviews that include multiple changes (e.g., dose of each drug, dosing interval, gestational age) simultaneously. Therefore, it is not possible to provide safety data specific to each individual change.

The changing of the dosing interval to 24-48 hours does not appear to increase the risk of serious fatal or nonfatal adverse events or to increase the risk of common adverse events associated with medical abortion.

Reviewer's Final Recommendation:

Based on the available evidence, changing the dosing interval between mifepristone and misoprostol to 24-48 hours is safe to approve, including for use in gestations up through 70 days.

2. Home administration of misoprostol

Currently, the Dosage and Administration section of labeling for Mifeprex requires that patients return to the healthcare provider on Day 3 (two days after ingesting Mifeprex) for misoprostol. The Applicant proposes that the label be changed to allow for home administration of the misoprostol. The Applicant reasons that all published US trials after the initial trial by Spitz et al²⁶, as well as numerous international trials, included distribution of misoprostol for self-administration at home with evidence of safe and effective medical abortion. The Applicant also emphasizes that women usually start having bleeding within two hours of administration of the misoprostol and home administration gives the opportunity for more privacy in the process.

The Applicant submitted many articles to support this change. See Table 8 for US and foreign studies that enrolled over 30,000 women who administered misoprostol at home. None of the studies directly compare home versus clinic/office administration of misoprostol. Most of the studies include protocols where all of the subjects take misoprostol at home. Gatter¹³ and Ireland¹⁵ reported separately on large numbers of clients of Planned Parenthood Los Angeles (13,373 and 13,221 clients respectively, though likely with some overlap, in 2010-2011), while Winikoff (2012¹⁹ and 2008²³), Grossman³⁶, Creinin²⁵ and Middleton²⁴ reported on smaller numbers of US subjects. Internationally, Goldstone²⁰ reported on 13,345 medical abortions, while Kopp Kallner⁶⁴, Løkeland⁶⁵, Chong (2012)⁴⁰, Bracken⁴⁹, Pena⁴⁴,

⁶⁴ Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. *Human Reprod* 2010;25(5):1153-1157.

⁶⁵ Løkeland M, Iversen OE, Engeland A, Økland I. Medical abortion with mifepristone and home administration of misoprostol up to 63 days' gestation. *Acta Obstet Gynecol Scand* 2014;93:647-653.

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Ngoc¹⁶, Louie¹⁴, Sanhueza Smith⁴⁸, Boersma²² and Lynd⁶⁶ report on smaller numbers of subjects. All of these studies have been reviewed above in Sections Deaths, Nonfatal Serious Adverse Events and Common Adverse Events. This information shows that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the original studies of clinic administration of misoprostol.

Swica et al⁵⁰ similarly conducted a non-randomized trial with 301 US women, 139 of whom chose home use of mifepristone and misoprostol and 162 of whom chose clinic administration of mifepristone followed by home use of misoprostol. The majority of women (74%) who chose home use took the mifepristone at the appointed 6-48 hour window; for those who took it at a different time than that planned with their provider, the median interval was 25 hours. Over 90% of women in both groups took the misoprostol at the scheduled time, and none waited past 72 hours to take the misoprostol. There were no significant differences in the mean number of days of work or school missed or dependent care needed. Most women made no additional calls (85% for home use group and 90% for office use group) or unscheduled visits to the doctor's office (96% for home use group and 99% for office use group).

The Applicant also submitted a commentary by Gold and Chong⁶⁷, in which they discuss benefits of home administration of Mifeprex and misoprostol. They cite the convenience of scheduling for women, the possibility of greater autonomy and privacy, the lack of burden on staff, and the safety.

Reviewer comment:

Home use of misoprostol has been evaluated as part of the proposed protocol in studies including well over 30,000 patients, as well as in dedicated studies of home use of mifepristone and misoprostol. The studies demonstrate that women take the misoprostol at the recommended time. The safety profile is acceptable, with rates of adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol. The studies, including those of home use of mifepristone and misoprostol, show increased convenience, autonomy and privacy for the woman, a smaller impact on their lifestyles, and no increased burden on the healthcare system. The safety data on the home use of misoprostol are adequate to support revision of labeling.

⁶⁶ Lynd K, Blum J, Ngoc NTN, Shochet T, Blumenthal PD, Winikoff B. Simplified medical abortion using a semi-quantitative pregnancy test for home-based follow-up. *Int J Gynecol Obstet* 2013;121:144-148.

⁶⁷ Gold M, Chong E. If we can do it for misoprostol, why not for mifepristone? The case for taking mifepristone out of the office in medical abortion. *Contraception* 2015;92:194-196.

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Reviewer's Final Recommendation:

Based on the available data, home use of misoprostol is safe to approve.

3. Repeat dose of misoprostol if needed.

The Applicant reasoned that studies include an option for a repeat dose of misoprostol to allow women to avoid a surgical procedure if possible and that this is a safe way to treat an incomplete medical abortion. The Applicant submitted two articles on the repeat use of misoprostol, one randomized trial and one systematic review, that were relevant to this safety review (other articles^{12, 17, 22} did not present safety data stratified by number of misoprostol doses). Only one randomized trial reviewed the safety of repeat misoprostol. Coyaji et al⁶⁸ conducted a randomized controlled trial of 300 women seeking medical abortion in India. After taking mifepristone, women in one group took 400 mcg misoprostol followed by placebo 3 hours later, while women in the other group took two doses of 400 mcg misoprostol 3 hours apart. As discussed in the efficacy portion of this review, there was no significant difference in the complete abortion rate between the groups; however, the repeat misoprostol reduced need for surgical intervention. Before discharge home, there was no significant difference in the adverse effects observed—similar percentages of women experienced cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). More women in the repeat dose arm experienced moderate to severe cramping than women in the single dose arm on Day 4 (24% versus 15%, $p=0.032$) and on Day 7 (10% versus 4%, $p=0.006$).

Gallo⁶⁹ performed a systematic review of data relating to the safety and efficacy of more than one dose of misoprostol after mifepristone for medical abortion. The search yielded three randomized controlled trials that studied medical abortion ≤ 63 days. The studies included doses of mifepristone ranging from 200 mg to 600 mg followed by misoprostol 6 to 48 hours later, in doses ranging from 400 mcg to 800 mcg via the oral, sublingual or vaginal routes. In two trials, all subjects received repeat misoprostol—in one, three hours later, while in the other study subjects received misoprostol twice a day for days 4-10. In the third trial, subjects only received repeat misoprostol if there was still a gestational sac present. The only side effects discussed in the trials were diarrhea, which was more common in those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported $<1\%$.

There is a good deal of literature on the use of misoprostol alone for medical abortion and in those regimens, doses of up to 800 mcg repeated in three hours have been

⁶⁸ Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? *BJOG* 2007;114:271-278.

⁶⁹ Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. *Contraception* 2006;74:36-41.

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used. In a study by Blum et al⁷⁰, misoprostol only, given as two doses of 800 mcg three hours apart, was compared to mifepristone-misoprostol medical abortion where only one dose of 800 mcg misoprostol was administered. The two groups had similar rates of nausea, vomiting, fever and chills. Subjects in the repeat misoprostol group had more diarrhea than in the mifepristone-misoprostol group (83.9% vs. 61.2%, p<0.001). Please see Section 7.4 Significant Adverse Events for additional discussion on safety concerns with repeat doses of misoprostol.

Reviewer comment:

There are few articles concerning the safety of repeat misoprostol after mifepristone administration. Generally, the success of mifepristone-misoprostol medical abortion renders the need for a second dose of misoprostol to be relatively uncommon. In studies of misoprostol alone given using a single repeat dose, there is an increased risk of the common adverse event of diarrhea. There have been rare reports of uterine rupture in women with a prior uterine scar who receive repeated doses of misoprostol.

Reviewer's Final Recommendation:

Based on the available data, the option for repeat misoprostol in women whose pregnancy has been terminated, but who have not completely expelled the pregnancy is safe and should be approved. For women whose pregnancy is ongoing at follow-up, surgical intervention is recommended, rather than repeated misoprostol. The rare reports of uterine rupture in women with a prior uterine scar who receive repeated doses of misoprostol is discussed in labeling.

4. Follow-up timing and method: follow-up is needed, but not necessarily in the clinic or licensed healthcare provider's office at 14 days after mifepristone administration

The Dosage and Administration section of the current approved label for Mifeprex stipulates that patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred. The Applicant acknowledges that follow-up is important to diagnose and treat complications, and to ensure complete abortion or identify ongoing pregnancies. However, the Applicant proposes to change the labeling to state that the provider should perform an assessment at 1-2 weeks, in order to broaden the timeframe and method used, to give patients and providers more flexibility and reduce loss to follow-up rates. Use of ultrasound, serum and urine pregnancy testing (semi-quantitative, and quantitative) and telephone calls have all been evaluated in the literature as options for follow-up of patients after medical

⁷⁰ Blum J, Raghavan S, Dabash R, Ngoc NTN, Chelli H, Hajri S, Conkling K, Winikoff B. comparison of misoprostol-only and combined mifepristone-misoprostol regimens for home-based early medical abortion in Tunisia and Vietnam. Int J Gynecol Obstet 2012;118:166-171.

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abortion. Grossman and Grindlay⁷¹ conducted a systematic review of the literature on alternatives to ultrasound for medical abortion follow-up. They identified eight studies, but found that outcomes of interest (ongoing pregnancy) were rare with medical abortion and not consistently defined across studies. Nonetheless, they found that serum hCG, a low sensitivity urine pregnancy test combined with a standardized assessment with multiple questions about women's symptoms, or standardized telephone follow-up, perhaps followed by high-sensitivity urine pregnancy test, all had sensitivities $\geq 90\%$ and negative predictive values (NPVs) $\geq 99\%$ and they resulted in a proportion of "screen positives (or women who had a self-assessment of ongoing pregnancy and had an unscheduled visit) $\leq 33\%$."

This reviewer analyzed relevant studies that were submitted by the Applicant and referenced in the Grossman and Grindlay assessment.⁷¹ Perriera et al²¹ conducted a prospective cohort study of 139 US women with ≤ 63 days gestation undergoing medical abortion at one center. Up to three attempts were made to phone subjects 7 days after taking mifepristone. The subjects were asked to confirm when they took misoprostol and generally to describe their experience. They were then asked a series of five standardized questions to assess for expulsion, including:

- 1 Did you have cramping and bleeding heavier than a period?
- 2 Did you pass clots or tissue?
- 3 What was the highest number of pads you soaked per hour?
- 4 Do you still feel pregnant now?
- 5 Do you think you passed the pregnancy?

If the clinician or the subject did not think the pregnancy had passed, the subject was asked to return to the center for an ultrasound within 7 days. If there was an ongoing pregnancy, women were offered additional misoprostol or a D&C. If the clinician and subject believed the pregnancy had passed, she was instructed to begin birth control or schedule a visit for injectable, implantable or intrauterine contraception. On Day 30, the subject was to perform a urine pregnancy test. Follow-up was obtained for 97.1% of subjects. Four subjects did not complete follow-up (2.9%)—one was never reached by phone, three were and two of them had positive pregnancy tests while one had an inconclusive test. These three never returned for an in-person visit and outcomes are not available on them. The sensitivity for correctly predicting an expelled pregnancy (completed abortion) was 95.9%, specificity was 50%, positive predictive value 97.5% and negative predictive value 37.5%. This study suggests that clinicians and subjects are almost always correct when they believe a pregnancy has passed. The loss to follow-up rate was not higher than for standard medical abortion follow-up.

Fiala et al⁷² compared hCG with ultrasound for verification of completed abortion in 217 women ≤ 49 days with intrauterine pregnancy in Scotland. Successful expulsions were

⁷¹ Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. *Contraception* 2011;83:504-510.

⁷² Fiala C, Safar P, Bygdeman M, Gemzell-Danielsson K. Verifying the effectiveness of medical abortion;

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consistent with a marked decline in hCG values at follow-up. Using 20% of the initial value as cut-off at follow-up gave a high sensitivity. It allowed correct diagnosis in 98.5% of the patients with successful expulsion. When 20% of the initial hCG value was used as cut-off, a positive predictive value for successful expulsion was 99.5%. If the reduction of the hCG level was less than 80%, the negative predictive value was 50% and further evaluation was warranted. By contrast, the reliability of ultrasound examination in diagnosing successful expulsion was 89.8%.

Lynd et al⁶⁶ studied 300 women at ≤ 63 days gestation who underwent medical abortion in Vietnam. Women were given mifepristone and sent home with misoprostol and a semi-quantitative urine pregnancy test, a urine cup, instructions and a questionnaire. They were to take the urine test, record their impression of the results and complete the questionnaire on the morning of an in-person follow-up visit 2 weeks after mifepristone administration. Fifty-four women (18.5%) still felt pregnant at the follow-up visit, but only 11 of the semiquantitative urine tests indicated ongoing pregnancies. All 11 correctly identified ongoing pregnancies, with 100% sensitivity and 89.7% specificity. Ten of the 11 women with an ongoing pregnancy understood in-person follow-up was necessary.

Similarly, Cameron et al⁷³ reported on 1791 women undergoing medical abortion in Scotland, 1,726 (96%) of whom chose self-assessment with a low-sensitivity urine pregnancy test, instructions on how to interpret it, and signs/symptoms of ongoing pregnancy. The rest of the women chose in-clinic follow-up with an ultrasound or a phone call. Eight women in the self-assessment group had ongoing pregnancies, but only four of them had a positive low-sensitivity pregnancy test at the appointed time—within 4 weeks. Of the four who did not follow up in 4 weeks, two had a positive or invalid pregnancy test within two weeks after the medical abortion and should have presented for care, and two reported their pregnancy test was negative and did not present for care. All had successful termination either with repeat medical dosing or surgical aspiration. Most women presented within four weeks, but two women presented only after two missed menses. The delayed follow-up was not different from that for an in-person visit or an ultrasound.

Reviewer comments:

While the number of articles is not extensive, they include almost 2,400 subjects. The Applicant demonstrates that alternatives to in-clinic follow-up are effective and safe, detecting most of the ongoing pregnancies so that women can get needed treatment. It appears that, using standardized questionnaires or instructions or a telephone call along with a low or high sensitivity pregnancy test, ongoing pregnancies can be detected allowing for further treatment. There is some loss-to-follow-up, but the rates do not appear to exceed those associated

ultrasound versus hCG testing. Eur J Obstet Gynecol Reprod Biol 2003;109:190-195.

⁷³ Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 2015;91:6-11.

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with a planned in-clinic follow-up. Women should be allowed to have an in-person visit if desired, but also allowed the flexibility of other options if desired.

It is important to note that since 2005, Planned Parenthood Federation of America has waived the follow-up visit if it poses undue hardships owing to distances from abortion facilities or other reasons, and women manage their follow-up with serial hCG testing.⁷⁴ From the clinical reviewers' perspective, this is safe and acceptable. We further note that the NAF 2015 guidelines (page 23) state the following:

“Success of the medical abortion must be assessed by ultrasonography, hCG testing, or by clinical means in the office or by telephone. If the patient has failed to follow-up as planned, clinic staff must document attempts to reach the patient. All attempts to contact the patient (phone calls and letters) must be documented in the patient’s medical record.”

The ACOG 2014 Practice Bulletin¹ on management of early MAB states “Follow-up after receiving mifepristone and misoprostol for medical abortion is important, although an in-clinic evaluation is not always necessary.” Several options for follow up without an office/clinic visit are discussed and no specific method or algorithm is definitely recommended (i.e., it is left to the discretion of the provider and patient).

Reviewer’s Final Recommendation:

Based on the available evidence, flexibility in the timing and method of follow-up is safe to approve.

7.5 Supportive Safety Results

7.5.1 Common Adverse Events

According to the currently approved Mifeprex label,⁷⁵ common adverse events include the following:

- Vaginal bleeding up to 16 days, with 8% of women experiencing bleeding up to 30 days. 4.8% of women in the original US trials and 4.3% in the original French trials required administration of uterotonic agents to control the bleeding. Only 1% of women required intravenous fluids and 1% required curettage. In the original French trials, 5.5% of women had a drop in hemoglobin of more than 2 g/dL.
- Abdominal pain in 96% of US women
- Uterine cramping in 83% of French women
- Nausea in 43-61%, vomiting in 18-26%

⁷⁴ Fjerstad M. Figuring out follow-up. Mife Matters. Planned Parenthood Federation of America/Coalition of Abortion Providers 2006;13:2–3.

⁷⁵ http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.htm

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- Diarrhea in 12-20%
- Headache in 2-31%
- Dizziness in 1-12%

A review of the literature submitted in the efficacy supplement, which includes Mifeprex at the proposed dose but also includes misoprostol administered buccally, vaginally or orally, reveals the following. Table 16 addresses bleeding that did not require transfusion (which is covered in Table 14: Transfusion by Gestational Age above), but was still significant in terms of requiring another intervention or in terms of a decrease in measured hemoglobin. Most of the studies include subjects up to 63 days' gestation, with the exception of Middleton 2005²⁴, which includes subject to 56 days, and Sanhueza Smith 2015⁴⁸ and Winikoff 2012¹⁹, which include subjects through 70 days.

Table 16: Bleeding and Cramping in Literature

Study	N	Maximal Gestational Age	Route of misoprostol administration	Adverse Event Rate (%)		
				Bleeding requiring intervention*	Bleeding with drop in hemoglobin > 2g/dL	Cramping/pain
Middleton 2005 ²⁴	216	56 d	buccal	4.2	NR	NR
Coyaji 2007 ⁶⁸					NR	87-89
Løkeland 2014 ⁶⁵				4.9	NR	96.6
Kopp Kallner 2010 ⁶⁴	395	63 d	vaginal	0.5	NR	NR
Pena 2014 ⁴⁴	971	63 d	Buccal	1.7	NR*	NR
Ngoc 2014 ¹⁶	1433	63 d	buccal	0.07	NR	NR
Gatter 2015 ¹³	13,373	63 d	buccal	1.8	NR	NR
Ireland 2015 ¹⁵	13,221	63 d.	buccal	1.8	NR	NR
Winikoff 2012 ¹⁹	729	70 d	buccal	1.1	NR	NR
Sanhueza Smith 2015 ⁴⁸	960	70 d	buccal	1.7	NR	NR

*Intervention includes aspiration or uterine evacuation, use of uterotonics, intravenous fluids

*NR=not reported

Source: NDA clinical reviewer table.

Reviewer Comments:

Given that Mifeprex and misoprostol are taken to terminate an intrauterine pregnancy, vaginal bleeding and cramping or abdominal pain are an expected

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and necessary part of the process; therefore, these should only be considered adverse events if the amount of bleeding or pain exceeds what would be expected for such a process. The rate of bleeding requiring intervention is low and ranges from 0.5% to 4.2%, with the rates in the largest studies being around 1.8%. Two articles parsed the bleeding requiring intervention by gestational age. In Sanhueza Smith et al.⁴⁸ the rate was 1.1% (7/622) among women \leq 56 days, 4.2% (8/190) in women 57-63 days and 1.4% (2/148) in women 64-70 days. In Gatter 2015¹³, the rate was 0.65-1.43% up to 49 days, 2.04% in women 50-56 days, and 2.49% in women 57-63 days. These differing numbers from the two studies do not reveal a trend toward bleeding requiring intervention with increasing gestational age, specifically even through 70 days.

No articles submitted discussed a drop in hemoglobin of > 2 g/dL, most likely because routine laboratory studies are not obtained in medical abortion unless anemia or a medical illness is reported or suspected. Also not surprisingly, pain and cramping are an expected part of the medical abortion process, so most studies do not comment on the percentage of women who experience this.

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Table 17: Common Adverse Events in Literature

Study	N	Maximal GA (days)	Route of Misoprostol	Adverse Event Rate (%)							
				nausea	vomiting	diarrhea	fever	chills	headache	dizziness	weakness
Middleton 2005 ²⁴	216	56 d	Buccal	70	37	36	42	NR	44	41	51
Blum 2012 ⁷⁰			buccal	45.9	37.8	61.2	28.2	30.6			NR
Coyaji 2007 ⁶⁸				1	0-2	NR*	NR	NR			NR
Kopp Kallner 2010 ⁶⁴	395	63 d	vaginal	87.1	57.3	6.3	26.3	NR	4.1	3.6	2-3.1
Louie 2014 ¹⁴	860	63 d	buccal	38-53	13-25	1-3	15-23†				NR
Pena 2014 ⁴⁴	971	63 d	buccal	NR	NR	7.8	8.9†	†	NR	NR	14.3
Creinin 2007 ²⁵	544	63 d	vaginal	9.4	5.7	4.8	10.3†	†	6.6	6.8	NR
Chong 2012 ⁴⁰	563	63 d	buccal	47	22	NR	33†	†	33	24	42
Winikoff 2012 ¹⁹	618	70 d	buccal	50.8	40.6	17.6	11.2	23.5	NR	NR	NR
Sanhueza Smith 2015 ⁴⁸	960	70 d	buccal	27	23	44.6	46†	†	14.3	9.7	21

GA = gestational age; *NR= not reported. † includes fever and chills, which were grouped together

Source: NDA clinical reviewer table.

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Reviewer comment:

The range of reported percentages for each adverse event is wide, with some studies reporting virtually no patients experiencing nausea, vomiting or diarrhea, while others report at least half of subjects suffering these side effects. Only the Winikoff 2012¹⁹ article parses out these side effects by gestational age (57-63 days versus 64-70 days). There is no statistically significant difference in the rates of any side effect between gestational age group except for vomiting, where 35.8% of women 57-63 days had vomiting and 45.7% of women 64-70 days did (p=0.008). It is hard to determine a value that could be used in labeling based on these wide variations, but the adverse events are common, expected and well-known with the medical abortion regimen and the ranges should be reported in labeling.

7.5.2 Laboratory Findings

Mifepristone with misoprostol is a well-established regimen for termination of pregnancy. Few laboratory tests are necessary before use of the regimen. Those that are commonly performed include confirmation of pregnancy (urine or serum pregnancy testing) as well as Rh testing (unless it has been previously documented), such that RhD immunoglobulin can be administered as indicated. Pre-medical abortion assessment of hemoglobin or hematocrit is indicated when anemia is suspected. Routine follow-up laboratory testing is also not indicated unless dictated by the patient's clinical condition, for example, heavy bleeding or signs of infection. Lab results are not typically reported in the literature, except for when studies look at decreases in hemoglobin related to bleeding.

7.5.3 Vital Signs

Vital signs are not typically reported in the literature on medical abortion.

7.5.4 Electrocardiograms (ECGs)

Mifepristone used with a prostaglandin analogue has been approved for medical termination of pregnancy since 1988 in France and subsequently in many countries around the globe. It has been well-established that doing an ECG prior to MAB is not standard procedure. It can be done if individual circumstances warrant its use. Literature does not typically report on ECGs.

7.5.5 Special Safety Studies/Clinical Trials

The pediatric studies are addressed in Section 7.6.3.

7.5.6 Immunogenicity

NA to this review

7.6 Other Safety Explorations

This section is not relevant to this application.

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7.6.1 Additional Safety Evaluations

7.6.2 Human Carcinogenicity

The Applicant submitted no new data on human carcinogenicity.

7.6.3 Human Reproduction and Pregnancy Data

As noted in the efficacy portion of this review, some women who use Mifeprex do have ongoing pregnancies. Most of these are treated with an aspiration or a surgical evacuation of the uterus; there is little information on outcomes of ongoing pregnancies not terminated by another method. At the time of approval of the drug, the Applicant agreed to two postmarketing commitments, including one to conduct a surveillance study of the outcomes of ongoing pregnancies. On January 11, 2008, the Applicant was released from this commitment due to the lack of an adequate number of women enrolled. The Applicant explained that the small number was due, in part, to the requirement that the patients consent to participation [*in the surveillance study*] after seeking a pregnancy termination.

A review of all of the articles submitted by the Applicant for outcomes of ongoing pregnancies after mifepristone administration yielded minimal information. There is one article reporting a case of a fetus with sirenomelia, a cleft palate and lip, micrognathia, and hygroma; this infant was born to a woman who had received mifepristone as RU 486 at 18 weeks and was reported to Roussel-Uclaf in France in 1989.⁷⁶ A prospective observational study⁷⁷ from fifteen French pharmacovigilance centers followed women exposed to mifepristone in the first trimester between 1997 and 2010. The study included pregnant women who sought counseling on mifepristone exposure from a pharmacovigilance center or Paris Teratology Information Service (TIS). A total of 105 pregnancies were exposed to mifepristone in the first trimester; 46 to mifepristone alone, and 59 to mifepristone and misoprostol. The mean gestational age at exposure was 7.9 weeks; 81% were exposed between weeks 5 and 9 of gestation. About 40% of patients received 200 mg of mifepristone while about 50% received 600 mg. Of the patients who received both mifepristone and misoprostol, 48 received repeat misoprostol with four receiving 1200–2000 mcg of misoprostol, a significantly higher dose than recommended. Among all exposed women, there were 94 live births (90.4%), 10 (9.6%) miscarriages (including one with a major malformation of major hydrocephalus associated with adductus thumb and a normal karyotype) and one patient had an elective termination of pregnancy for the subsequent diagnosis of trisomy 21. Eight of the ten miscarriages occurred in the mifepristone-only group; however, after potential confounding factors such as maternal age, gestational age at inclusion,

⁷⁶ Pons JC, Papiernik E. Mifepristone teratogenicity. *Lancet* 1991;338(8778):1332-3.

⁷⁷ Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. *BJOG* 2013;120:568–575.

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drug exposure, and mifepristone dose were controlled for by logistic regression, the rate of miscarriage did not differ across mifepristone only versus mifepristone-misoprostol groups ($p= 0.08$). Among the live births, the mean gestational age at delivery was 39.5 weeks and there was no difference in birth weights between groups. The overall rate of major congenital malformations among the 95 examinable cases was 4.2% (95% CI 1.2–10.4%), with two cases among 38 patients exposed to mifepristone alone, and two cases among 57 patients exposed to both mifepristone and misoprostol. Three of the four major congenital malformations occurred with exposure to 600 mg of mifepristone, while one occurred in exposure to 400 mg of mifepristone. The malformations included:

- Claude Bernard–Horner syndrome with stridor
- Hydrocephalus with triventricular dilatation and adductus thumb (miscarriage patient noted above)
- Möbius syndrome
- Retrognathism, slight cleft palate, trismus, swallowing disorder, club foot with four toes, incomplete genital development and mild hypoplasia of the cerebellar vermis

The authors posit that the cases of major malformations in patients exposed to mifepristone alone could be explained by associated medical conditions, for example, the case of congenital Claude Bernard Horner syndrome could have been related to traumatic vaginal delivery of a high birth weight newborn, a well-recognized cause of this syndrome, while the spontaneously aborted hydrocephalic fetus may have been caused by streptococcus B chorioamnionitis, which was subsequently confirmed on pathological examination, or be an X-linked hydrocephalus. The authors also note that the two cases of major malformations in patients exposed to both mifepristone and misoprostol were consistent with malformations described after exposure to misoprostol alone. The authors concluded that major malformations after first-trimester exposure to mifepristone is only slightly higher than the expected 2–3% rate in the general population, which was reassuring regarding the risk evaluation for continuation of pregnancy after mifepristone exposure.

There are reports that misoprostol can result in congenital anomalies when used during the first trimester, including defects in the frontal or temporal bones, limb abnormalities with or without Mobius syndrome.¹ The Korlym label notes in Important Safety Issues with Consideration to Related Drugs: “In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.”

Reviewer Comment:

There are anomalies associated with the use of misoprostol in the first trimester. The risk of teratogenic effects with a continued pregnancy after a failed pregnancy termination with Mifeprex in a regimen with misoprostol is unknown. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with Mifeprex in a regimen with misoprostol, but it is not clear if this just represents the usual background rate of birth defects.

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As discussed above, FDA requested at the time of initial approval that the Applicant conduct a surveillance study of the outcomes of ongoing pregnancies. The Applicant was subsequently released from this commitment because it had been unable to enroll a sufficient number of women with ongoing pregnancies after an attempted medical abortion in the surveillance study.

7.6.4 Pediatrics and Assessment of Effects on Growth

The Applicant submitted no new data on assessment of effects on growth in pediatric patients. The Applicant did submit data on efficacy and safety of medical abortion in adolescents, using the proposed regimen of 200 mg oral Mifeprex followed by 800 mcg buccal misoprostol 24-48 hours later at home, in order to satisfy requirements for PREA. Gatter et al (2015)¹³ included data on 322 adolescents. (b) (6), (b) (4)

The adolescent efficacy was similar to that of all older women; this implies that compliance in taking the misoprostol dose properly at home was also acceptable. The study included adolescents aged 11-16 per Table 18 below:

Table 18: Age of Adolescents Undergoing Medical Abortion

Age	# Subjects
11	1
12	1
13	2
14	20
15	82
16	216

Source: (b) (6), (b) (4) NDA 20687s20

(b) (4), (b) (6) As is evident in the table, no adolescents had a hospitalization, severe infection or hemorrhage which required a transfusion.

Table 19: Serious Adverse Events in Adolescents vs. Adults

	Under 17	17+	All
Transfusion	0.00% (0/251)	0.03% (4/13,122)	0.03% (4/13,373)
Hospitalization	0.00% (0/251)	0.05% (7/13,122)	0.05% (7/13,373)
Infection	0.00% (0/251)	0.02% (2/13,122)	0.01% (2/13,373)

Source: (b) (6), (b) (4) NDA 20687s20

In 2011, Niinimäki et al⁵⁴ published a retrospective cohort study of the Finnish abortion registry from 2000-2006, in which they evaluated the rates of adverse events in 3,024

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adolescents and 24,006 adult women undergoing medical abortion (regimen unspecified). The study population included women \leq 20 week's gestation; 84.6% of the adolescents were \leq 12 weeks, while 86.6% of the adults were \leq 12 weeks. Adolescents ranged in age from 13-17, with a mean age of 16.1 years. The study showed that after adjustment for parity, previous abortion, marital status, types of residence, duration of gestation and year of abortion, in adolescents, the adjusted ORs were significantly lower for hemorrhage (0.87, 95% CI 0.77 to 0.99), incomplete abortion (0.69, 95% CI 0.59 to 0.82) and surgical evacuation (0.78, 95% CI 0.67 to 0.90) compared to adults. There was no significant difference in the OR for infection (0.97, 95% CI 0.73 to 1.30).

Phelps⁵³ had previously conducted a pilot study in 28 adolescents aged 14-17, at \leq 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. As reported in Section Subpopulations, 100% of study subjects had a complete abortion, with five not requiring misoprostol. There were no serious adverse events. Subjects noted common expected adverse events including bleeding (100%), cramping (95%), nausea (62%), and vomiting (43%).

It is also important to consider adherence to the proposed regimen (including taking misoprostol at a location other than the clinic) and adherence to follow-up among adolescents versus adults.

There are no data specifically comparing adherence to the regimen among adolescents <17 with women ≥ 17 years old. The Gatter¹³ study clearly demonstrates the efficacy and safety is the same for both age groups, suggesting that there is no clinically significant difference in adherence to the regimen between age groups. The Goldstone²⁰ article included 8 subjects aged 14 and 931 subjects aged 15-19. The efficacy and safety are not separated out by age; however, all subjects did take the proposed regimen and overall efficacy and safety is reassuring, indicating that adolescents and adults alike likely did adhere to the mifepristone and misoprostol regimen in a safe and effective way.

Regarding adherence to follow-up, four articles included 346 subjects <17 years old. Ngoc¹⁶ is based in Vietnam and Cameron⁷³ is based in Scotland, while Gatter¹³ and Horning⁷⁸, are US-based studies. (b) (4), (b) (6)

. The difference in the follow-up rate for the combined data is 6.5%. The Gatter study accounts for 85% of all patients being compared. The difference in follow-up adherence is not clinically relevant as there is no difference in efficacy between the two age groups.

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Table 20: Adherence to Follow-Up Among Adolescents vs. Adults

	<17 years old			≥17 years old		
	N	# Adherent	Adherence %	N	# Adherent	Adherence %
Gatter ¹³	322	251	78.0%	15,517	13,122	84.6%
Cameron ⁷¹	5	4	80.0%	607	516	85.0%
Ngoc ¹⁶	1	1	100.0%	1,406	1,345	95.7%
Horning ⁷⁸	18	16	88.9%	846	648	76.6%
TOTAL	346	272	78.6%	18,376	15,631	85.1%

Reviewer Comment:

Medical abortion in adolescents appears to be at least as safe, if not safer, as in adult women. Adolescents appear able to comply with the regimen, including use of misoprostol outside of the clinic setting, as well as with alternative follow-up methods. These data support the safety of Mifeprex in adolescents and satisfy requirements for PREA. No information on safety and efficacy of use in premenarchal girls is required, as the medication is not indicated in that subset of the pediatric population.

Reviewer's Final Recommendation:

The available evidence supports that Mifeprex and the new proposed dosing regimen are safe to use in adolescents.

7.6.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant submitted no new data on overdose, drug abuse potential withdrawal and rebound.

7.7 Additional Submissions / Issues

Summary of additional changes in labeling that may affect safety of Mifeprex

1. Change in labeled time for expulsion from 4-24 hours to 2-24 hours

The Applicant proposes to change the time to expulsion described in the labeling from 4-24 hours to 2-24 hours post misoprostol to more accurately reflect the data and real-life experiences with the drug. The Applicant reasons that in the large US trial upon

⁷⁸ Horning EL, Chen BA, Meyn LA, Creinin MD. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. *Contraception* 2012;85:402-407.

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which labeling is based (Spitz, 1998²⁶), the median time to expulsion was 4 hours. Indeed, in that study, women were observed for several hours after misoprostol administration, and during the four hours of observation, 49% of the women expelled the products of conception, and 60% had by the fifth hour. Several studies are provided to corroborate this. Only one uses buccal misoprostol; however, the misoprostol was administered within 5 minutes of the Mifeprex, not at the 24-48 hour interval as proposed in this supplement. Nonetheless, in this trial, Lohr⁷⁹ found the median time to onset of cramping to be 2 hours (range 10 minutes to 13 hours) and bleeding to be 3 hours (range 9 minutes to 11 hours). This shorter duration to expulsion is also seen in several other pilot studies submitted where subjects took vaginal misoprostol immediately or within 6-8 hours of mifepristone. If the focus is shifted to the randomized controlled studies that report times to onset of bleeding and cramping and include vaginal misoprostol, we find data confirming the timing of expulsion in the 2-24 hour window proposed by the Applicant. Creinin²⁵ noted a median time to onset of cramping of 1.7 hours and to onset of bleeding of 2 hours after misoprostol (administered 24 hours after Mifeprex). In a similar study⁸⁰ comparing misoprostol administered 24 vs. 6-8 hours after Mifeprex, the median time to onset of cramping was 1.5 hours and to bleeding was 2 hours in women with misoprostol given 24 hours after Mifeprex.

Reviewer comment:

The data from vaginal and buccal administration of misoprostol around 24 hours after mifepristone support the assertion that bleeding and cramping begin before the 4 hour mark that is currently labeled. Therefore the label should be revised to make this clearer. Median times seem to be around 1.5 to 2 hours. It is reasonable to label the time to expulsion 2-24 hours, but it could be labeled as beginning even earlier. A clearer label will help providers better counsel patients and patients can better select an appropriate time frame within the 24-48 hour window to take their misoprostol and can be prepared when the expulsion starts.

Reviewer's Final Recommendation:

Based on the available evidence, it is acceptable to revise the label so that it notes that the time to expulsion after misoprostol dosing is 2-24 hours.

2. Use of the term “ (b) (4) ”

The Applicant proposes to use the term “ (b) (4) ” in place of all other terms in labeling and in the REMS materials, for consistency and (b) (4)
 (b) (4) The Applicant

⁷⁹ Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD. Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study. *Contraception* 2007;76:215-220.

⁸⁰ Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004;103:851-859.

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submitted an article demonstrating that nurse practitioners, certified nurse midwives and physician assistants can safely provide aspiration abortion.⁸¹ The Division asked the Applicant to provide articles specifically addressing the provision of medical abortion services by non-physician practitioners, since that is the issue at hand.

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies took place in varying settings (urban, rural, international, low resource). The efficacy results are discussed in Section 6.1.10.

Regarding the safety of medical abortion provided by non-physician health care providers, a systematic review by Renner⁸² identified five studies with a total of 8,908 subjects. A RCT in Nepal included 1,104 of those subjects, comparing medical abortions by nurses or auxiliary nurse midwives with those offered by physicians. Outcome data on 1,077 women showed no serious complications (hemorrhage requiring transfusion or condition necessitating hospitalization) and the rate of ongoing pregnancy or incomplete abortion did not vary by physician versus midlevel provider. Also in Nepal, Puri et al⁸³ described training female community health volunteers to provide education, and training auxiliary nurse midwives to provide medical abortion in intervention districts, and compared knowledge and medical abortion outcomes with those in neighboring districts where there were no interventions. Medical abortions were performed on 307 women in the intervention areas and 289 women in the comparison areas. There were five incomplete abortions (1.6%) in the intervention areas, treated with manual vacuum aspiration by the auxiliary nurse midwives, and 7 (2.4%) incomplete abortions in the comparison areas. The difference was not statistically significant. Kopp Kallner⁸⁴ conducted a randomized controlled equivalence trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. The trial showed fewer complications for the nurse midwife group, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, p=0.14).

⁸¹ Weitz TA, Taylor D, Desai S, Upadhyay UD, Waldman J, Battistelli MF, Drey EA. Safety of aspiration abortion performed by nurse practitioners, certified nurse midwives, and physician assistants under a California legal waiver. *Am J Public Health* 2013;103:454-461.

⁸² Renner R-M, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care: a systematic review. *BJOG* 2013;10:23-31.

⁸³ Puri M, Tamang A, Shrestha P, Joshi D. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. *Reproductive Health Matters* 2015;Suppl(44):94-103.

⁸⁴ Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomized controlled equivalence trial. *BJOG* 2015;122:510-517.

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There were no serious complications and no blood transfusions in the study. There was no difference in unscheduled visits. Nurse midwives did call for more second opinions (26%) versus doctors (4%). Olavarrieta⁸⁵ conducted a randomized controlled non-inferiority trial in Mexico City abortion clinics. Eight physicians and seven nurses who had not previously independently provided medical abortion care received 1.5 weeks of training. A total of 1,088 women were randomized to two groups of providers. Nurses were not found to be inferior to physicians in the provision of abortion care. There was only one serious adverse event in the physician group, a woman requiring admission and surgical aspiration for heavy bleeding. Nurses requested consultation with an experienced obstetrician in 9 cases, whereas physicians requested consultation only twice.

Reviewer Comments:

The Applicant provided data from over 3,200 women in randomized controlled trials and data on 596 women in prospective cohorts comparing medical abortion care by physicians versus nurses or nurse midwives. The studies were conducted in varying settings (international, urban, rural, low-resource) and found no differences in efficacy, serious adverse events, ongoing pregnancy or incomplete abortion between the groups. Two studies did show that nurses or nurse midwives called for more second opinions than physicians, but these numbers were a small portion of the total subjects included.

Midlevel providers in the United States, such as nurse practitioners, nurse midwives and physician assistants currently provide family planning services and abortion care, including medical abortion care, under the supervision of physicians. The data here demonstrate that it would be safe to allow healthcare providers who are licensed to prescribe medications and who meet the criteria in the REMS to become certified to provide medical abortion care with Mifeprex and misoprostol. Midlevel providers are already practicing abortion care under the supervision of physicians, and the approved labeling and the REMS Prescriber's Agreement already stipulate that prescribers must be able to refer patients for additional care, including surgical management if needed. Therefore, facilities that employ midlevel prescribers already have an infrastructure in place for consultation and referral.

Reviewer's Final Recommendation:

Based on the available evidence, it is safe for midlevel providers to administer medical abortion. The term in the revised Prescriber Agreement Form will be "a healthcare provider who prescribes." Per the review by the (b) (6) (b) (6) dated March 29, 2016, this term provides an accurate

⁸⁵ Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousiequez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ 2015;93:249-258.

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representation of the varied practitioners who are prescribers, while at the same time using language that is consistent with statute. We concur with the review.

3. Removal of references to “Under Federal Law” from the Prescriber’s Agreement

The Applicant requests removal of the phrase “under Federal law” from the Prescriber’s Agreement portion of the REMS materials. The phrase appears in two places:

- “Under Federal law, Mifeprex must be provided by or under the supervision of a licensed 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.”
- “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 Applicant rationalizes that all of the conditions of Mifeprex approval, including the REMS, are under Federal law and that the statement is redundant and are no more subject to Federal law than the other conditions of approval.

Reviewer comment:

A rationale for the original inclusion of the phrase “Under Federal law” cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and can be removed from the Prescriber’s Agreement.

Reviewer’s Final Recommendation:

The term “under Federal law” can be removed from the Prescriber’s Agreement.

4. Addition of misoprostol to the indication statement

The Indication and Usage section of the currently approved labeling is as follows:

“Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days’ pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation

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occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination.

Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 mcg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS)."

The Applicant proposed two alternative indication statements, both of which include reference to misoprostol:

(b) (4)

Or

(b) (4)

The Applicant provides the rationale that:

- the two drugs are used in combination and placing misoprostol in the indication statement early on in labeling gives it greater prominence and highlights the importance of completing the full treatment regimen

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- the mention of misoprostol enhances the goal of labeling, which is to give healthcare providers information necessary for safe and effective use of Mifeprax.

Subsequently on February 25, 2016, the Applicant proposed (b) (4) (b) (4) gestational age through 70 days, based on the literature already submitted.

Reviewer comment:

We recommend that the Indication Statement read:

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

The rationale for this is that:

- **All supporting data are based on the combined regimen**
- **Inclusion of misoprostol in the Indication Statement would be consistent with the rest of Mifeprax labeling and with current medical practice**
- **It would be consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include “Information if drug is to be used only in conjunction with another therapy.”**

Reviewer’s Final Recommendation:

Misoprostol should be included in the Indication Statement for Mifeprax.

8 Postmarket Experience

A comprehensive review of the adverse events associated with Mifeprax from September 28, 2000 through November 17, 2015, performed by (b) (6), (b) (6), yielded the following information on reported deaths. Regarding the US cases, there were 17 reported deaths. Deaths were associated with sepsis in eight of the 17 (seven cases tested positive for *Clostridium sordellii*, one case tested positive for *Clostridium perfringens*). Seven of the eight fatal sepsis cases reported vaginal misoprostol use; one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a case of delayed onset toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. The autopsy report on the ninth death became available to the Agency and was reviewed on December 2, 2015. It showed the woman died of pulmonary emphysema.

There were 11 additional deaths in women in foreign countries who used mifepristone for medical termination of pregnancy. These fatal cases were associated with the

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following: sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial; sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; “multivisceral failure;” thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes, a jejunostomy feeding tube, and severe cystic fibrosis; and a case of *Clostridium sordellii* sepsis (from a published literature report).

Reviewer Comments:

While an exact rate of death with use of mifepristone cannot be calculated from this information, given that there have been over 2.5 million uses of Mifeprex by US women since its marketing in 2000, the number of deaths is very low. Moreover, half of the deaths were associated with *C. sordellii* sepsis. Seven out of 8 of these cases occurred in women who used misoprostol via the vaginal route while one used buccal misoprostol. Since at least 2006, PPFA (comprising the majority of US medical abortion providers) switched its national guidelines to avoid vaginal administration of misoprostol (even though the data did not find a causal relationship).²³ Although the possibility that Mifeprex might increase the likelihood of infection by adversely affecting immune system function has been raised, the overall event rate of serious infections does not support this.

Since 2009, there have been no *C. sordellii* deaths associated with medical abortion in the US. This reviewer finds that the postmarketing data on deaths associated with medical abortion demonstrate low numbers and an improved safety profile with the buccal route of misoprostol administration as compared with the vaginal route.

The review by (b) (6) (b) (6) also yielded the following

Table 21 summarizing hospitalizations, blood loss requiring transfusions, and severe infections.

Table 21: US Postmarketing AEs- Mifepristone for Medical Abortion

Date ranges of reports received	09/28/00 [†] -10/31/12	11/1/12 - 04/30/14 [‡]
Cases with any adverse event	2740	504
Hospitalized, excluding deaths	768	110
*Experienced blood loss requiring transfusions [§]	416	66
Infections (*Severe infections [¶])	308 (57)	37 (5)

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† U.S. approval date.
‡ FDA implemented FAERS on September 10, 2012, and migrated all of the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. As a result of this change, it is not recommended to calculate a cumulative number when reviewing the data provided in Table 5.
* The majority of these women are included in the hospitalized category in Table 5.
§ As stated in the approved Mifeprex (mifepristone) labeling, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.
|| This category includes endometritis (inflammation resulting from an infection 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 and gonorrhea, cystitis, and toxic shock syndrome not associated with a pelvic infection.
¶ This subset of infections includes cases that were determined to be severe based on medical review of the available case details. Severe infections generally result in death or hospitalization for at least 2-3 days, require intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, or have other physical or clinical findings, laboratory data, or surgery that suggest a severe infection.

Source: Review by (b) (6) (b) (6) (b) (6) dated 08/27/2015.

The (b) (6) review also describes ectopic pregnancies:

Table 22: US Postmarketing Ectopic Cases- Mifepristone for Medical Abortion

Date Range of Cumulative Reports	9/28/2000-10/31/14*	11/1/14-4/30/2015
Ectopic Pregnancies†	79	10

* U.S. approval date

† Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

Source: (b) (6) (b) (6) (b) (6) Mifepristone U.S. Post-marketing Adverse Events 6 month Update Summary through 04/30/2015, dated 08/20/2015.

Reviewer comment:

While exact rates cannot be calculated, as these reports are spontaneously generated, a few conclusions can be drawn from the information provided:

- **Given that there have been over 2.5 million uses of Mifeprex by US women since its marketing in 2000, including the use of the proposed dosing regimen and extended gestational age at many clinic/office sites, the numbers of hospitalizations, severe infections, blood loss requiring transfusion and ectopic pregnancy will likely remain acceptably low.**
- **The numbers of each of these adverse events appears to have remained steady over time, with a possible decrease in severe infections.**

A discussion of a (b) (6) review of uterine rupture is found in the Section Significant Adverse Events.

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(b) (6) identified another safety signal in a review dated January 27, 2016. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. A literature search did not reveal any case reports of either adverse event with mifepristone. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of the various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema.

In the case of anaphylaxis, it was reported that the patient experienced an anaphylactic reaction three hours after mifepristone administration; however, co-administration of doxycycline was also documented. Because both mifepristone and doxycycline were discontinued simultaneously, the exact cause of the anaphylactic reaction cannot be determined.

Regarding angioedema, five of the six cases noted a time-to-onset within 24 hours of mifepristone administration for the termination of pregnancy, with no additional suspect medications reported. The remaining case of angioedema with mifepristone reported a time-to-onset of approximately one week in a Cushing's syndrome patient with a complex medical history and multiple concomitant medications; however, this case noted both a positive dechallenge and rechallenge upon sole re-introduction of mifepristone therapy. Evaluation of these FAERS cases provides supportive evidence of a drug-event association between angioedema and mifepristone. The (b) (6) reviewer recommends the inclusion of anaphylaxis and angioedema within the Mifeprex labeling, specifically to the Contraindications and Adverse Reactions Postmarketing Experience sections.

Reviewer Comment:

There does appear to be an association with angioedema and mifepristone administration. The reviewers agree with inclusion of anaphylaxis and angioedema in the labeling for Mifeprex and with continued pharmacovigilance for anaphylaxis.

9 Appendices

9.1 Literature Review/References

This NDA review obviously involved an extensive review of resources and the peer-reviewed medical literature that was pertinent to the requested changes of the Applicant. Such sources are noted throughout the review in footnotes. A detailed Reference List is found in Appendix 9.6.

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9.2 Labeling Recommendations

The package insert (PI) for this product was submitted in the Physician Labeling Rule (PLR) format. Although not required for this supplement, Section 8 was revised in accord with the Pregnancy and Lactation Labeling Rule (PLLR). Section 17 Patient Counseling Information was also revised to be compatible with the new dosing regimen and follow-up. Major changes were made that updated the labeling with new safety and efficacy information, especially in two areas:

- 1) 6.1 Clinical Trials Experience in the section 6 Adverse Reactions
- 2) 14 Clinical Studies

Changes were also made in the patient package insert (PPI) and Medication Guide for the product. These format and content updates marked a significant improvement in the label. Agreement on the Final Approved label was reached with the Applicant on March 29, 2016.

Reviewer comment:

The new dosing regimen was based on the extensive number of articles submitted by the Applicant from the peer reviewed medical literature. The revised label used the new PLR format which is a complete change from the previous style. This meant that the newly approved label was extensively rewritten and much improved from the old format.

9.3 Advisory Committee Meeting

An Advisory Committee met in 1996 to discuss the approval of mifepristone plus misoprostol for medical termination of early pregnancy. There has been extensive US (15+ years with over 2.5 million uses) and global use (27+ years) of mifepristone and misoprostol for the medical termination of early pregnancy. No special external consultations were requested by the review Divisions. The FDA determined that the efficacy supplement did not raise complex scientific or other issues that would warrant holding an advisory committee meeting before approval of the supplement.

9.4 (b) (6) ((b) (6) Meeting

As noted in Product Regulatory Information, Mifeprex was originally approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, in accordance with § 314.520 of subpart H, FDA restricted the distribution of Mifeprex and required that Mifeprex be provided by or under the supervision of a physician who met certain qualifications. Further, practitioners had to complete a Prescriber's Agreement, provide patients with a Medication Guide and have patients sign a Patient Agreement. Mifeprex was included on the list of products deemed to have in effect an approved REMS⁸⁶ under section

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505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of FDA Amendments Act (FDAAA) of 2007. A formal REMS proposal was submitted by Danco and approved on June 8, 2011, with the essential elements unchanged. The REMS included:

- Medication Guide
- Elements to Assure Safe Use (ETASU):
 - Prescribed only by certified prescribers (ETASU A; includes a Prescriber's Agreement)
 - Dispensed only in certain healthcare settings (ETASU C)
 - Dispensed with documentation of safe use conditions (ETASU D; includes a Patient Agreement)
- Implementation System
 - Distributed only by certified distributors

Following this approval, two REMS assessment reports were completed. The Year 1 assessment was completed on June 1, 2012 and the Years 2-4 assessment was completed on June 2, 2015. Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

On July 16, 2015, the Applicant submitted a revised REMS as part of the efficacy supplement. The proposed modifications included:

- Prescriber's Agreement Form
 - Remove "Under Federal law"
 - Replace "physician" with "(b) (4)"

The Agency determined that broader review of the REMS was warranted concurrently with the efficacy supplement because some proposed changes in labeling dovetail with proposed changes to the REMS, and the documents should remain consistent with each other. Further, extensive review of the postmarketing experience based on the literature submitted to support the efficacy supplement, and pharmacovigilance, suggested that certain components of the REMS may no longer be necessary to assure safe use of Mifeprex.

In light of the efficacy review, upon assessment of the proposed modifications, (b) (6) concurs with (b) (6) recommendations that:

- Removal of "under Federal law" from the Prescribers' Agreement was acceptable (see discussion in Additional Submissions / Issues)
- The term "healthcare providers who prescribe" is preferable to (b) (4) (see discussion in Additional Submissions / Issues)

(b) (6) and (b) (6) also proposed the following modifications:

- Removal of the Medication Guide from the REMS (will remain a part of labeling and must be distributed by the prescriber as required under 21 CFR part 208)
- Removal of the Patient Agreement form - Documentation of Safe Use (ETASU D)

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- Revision of the Prescriber's Agreement form
- Revision of the REMS goal to reflect above changes

FDA considered the need for the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." FDA has received such reports for 15 years; the safety profile of Mifeprex is well-characterized, no new safety concerns have arisen in recent years, and the known serious risks occur rarely. For this reason, the reviewers do not believe ongoing reporting of all of the specified adverse events is warranted. The Applicant will still be required by law, as is every NDA holder, 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.

(b) (6) and (b) (6) met with the (b) (6) (b) (6) (b) (6) on January 15, 2015, to discuss the proposed modifications. The (b) (6) concurred with the removal of the term "under Federal law" and with use of the term "healthcare providers who prescribe." The (b) (6) also concurred with the removal of the Medication Guide (MG) from the REMS, though the document would remain a part of labeling. FDA has been maintaining MGs as labeling but removing them from REMS when, as here, inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks, such as when the MG is redundant and not providing additional use or information to the patient about the risk(s) the REMS is intended to mitigate. This is consistent with ongoing efforts to streamline REMS by allowing for updates to the MG without need for a REMS modification. (b) (6) and the (b) (6) had subsequent interactions and on February 23, 2016, the (b) (6) concurred with the decision to remove the Patient Agreement (ETASU D) from the REMS. This decision was based on the following rationale:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance
- Established clinical practice includes patient counseling and documentation of Informed Consent, and, more specifically with Mifeprex, includes counseling an all options for termination of pregnancy, access to pain management and emergency services if needed. The National Abortion Federation (NAF) provides clinical practice guidelines^{Error! Bookmark not defined.} and evidence shows that practitioners are providing appropriate patient counseling and education; a survey published in 2009 demonstrated that 99% of facilities surveyed provided pre-abortion counseling with patient education.⁸⁷ This indicates that the Patient Agreement form is duplicative and no longer necessary to ensure that the benefits of the drug outweigh the risks.

⁸⁷ 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.

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- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines cover the safety information that is duplicated in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the supervision of a certified prescriber at the time the patient receives treatment with Mifeprex.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

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9.4 Abbreviations**List of Abbreviations**

Abbreviation	Term
ACOG	American College of Obstetrics and Gynecology
APHA	American Public Health Association
CDER	Center for Drug Evaluable and Research
CDRH	Center for Devices and Radiological Health
(b) (6)	(b) (6)
FU	follow up
GA	gestational age
IRB	Institutional Review Board
LFU	lost to follow up
LMP	last menstrual period
MAB	medical abortion
MG	Medication Guide
Miso	misoprostol
NA	not applicable
NAF	National Abortion Federation
NDA	New drug application
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
PPFA	Planned Parenthood Federation of America
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategies
ROA	route of administration
(b) (6)	(b) (6)
SAB	surgical abortion
WHO	World Health Organization

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FDA label for ella:

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

FDA Label for Korlym:

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

FDA label for Mifeprex:

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Clinical Review

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9.6 Mifepristone Approvals Globally	2003		2015
	<input type="checkbox"/>	Estonia	<input type="checkbox"/> Canada
	2004		
	<input type="checkbox"/>	Guyana	
	<input type="checkbox"/>	Moldova	
1988	2005		
<input type="checkbox"/> China	<input type="checkbox"/>	Albania	
<input type="checkbox"/> France	<input type="checkbox"/>	Hungary	
1991-	<input type="checkbox"/>	Mongolia	
<input type="checkbox"/> UK	<input type="checkbox"/>	Uzbekistan	
1992	2006		
<input type="checkbox"/> Sweden	<input type="checkbox"/>	Kazakhstan	
1999	2007		
<input type="checkbox"/> Austria	<input type="checkbox"/>	Armenia	
<input type="checkbox"/> Belgium	<input type="checkbox"/>	Kyrgyzstan	
<input type="checkbox"/> Denmark	<input type="checkbox"/>	Portugal	
<input type="checkbox"/> Finland	<input type="checkbox"/>	Tajikistan	
<input type="checkbox"/> Germany	2008		
<input type="checkbox"/> Greece	<input type="checkbox"/>	Nepal	
<input type="checkbox"/> Iceland	<input type="checkbox"/>	Romania	
<input type="checkbox"/> Israel	2009		
<input type="checkbox"/> Luxembourg	<input type="checkbox"/>	Cambodia	
<input type="checkbox"/> Netherlands	<input type="checkbox"/>	Italy	
<input type="checkbox"/> Russia	2010		
<input type="checkbox"/> Spain	<input type="checkbox"/>	Zambia	
<input type="checkbox"/> Switzerland	2011		
2000	<input type="checkbox"/>	Ghana	
<input type="checkbox"/> Norway	<input type="checkbox"/>	Mexico	
<input type="checkbox"/> Taiwan	<input type="checkbox"/>	Mozambique	
<input type="checkbox"/> Tunisia	2012		
<input type="checkbox"/> US	<input type="checkbox"/>	Australia	
2001	<input type="checkbox"/>	Bangladesh	
<input type="checkbox"/> New Zealand	<input type="checkbox"/>	Ethiopia	
<input type="checkbox"/> South Africa	<input type="checkbox"/>	Kenya	
<input type="checkbox"/> Ukraine	2013		
2002	<input type="checkbox"/>	Azerbaijan	
<input type="checkbox"/> Belarus	<input type="checkbox"/>	Bulgaria	
<input type="checkbox"/> Georgia	<input type="checkbox"/>	Czech Republic	
<input type="checkbox"/> India	<input type="checkbox"/>	Slovenia	
<input type="checkbox"/> Latvia	<input type="checkbox"/>	Uganda	
<input type="checkbox"/> Serbia	<input type="checkbox"/>	Uruguay	
<input type="checkbox"/> Vietnam			
	2014		
	<input type="checkbox"/>	Thailand	

Clinical Review

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/s/

[Redacted] (b) (6)
03/29/2016

[Redacted] (b) (6)
03/29/2016

[Redacted] (b) (6)
03/29/2016

I concur with [Redacted] (b) (6) conclusions and recommendations for approval of this efficacy supplement.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 020687

Applicant: Danco Labs

Stamp Date: May 29, 2015

Drug Name: Mifeprex
(Mifepristone)NDA/BLA Type: supplement
#020

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			Paper submission.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?			x	
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?		x		The applicant has not provided module 2 summaries as this is an NDA based on published literature. The applicant has provided a justification summarizing the evidence of safety and efficacy for the proposed changes.
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		See comment for 8.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		See comment for 8.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Scientific justification-30 pg document
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	x			(b) (2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	x			The sponsor provides a bridge from the approved product to the proposed changes, with literature based

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					transfusion, infection requiring IV antibiotics, death). There are another 5 articles with limited safety information and 6 articles with safety information, but using different dosing regimens (e.g. not the approved or proposed new regimen).
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			x	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			x	There is no mapping of investigator terms to preferred terms. AE's were variably ascertained; 21 studies include data on SAE's of interest, 7 have limited safety information, 6 have safety information on the approved dosing regimen. Some 7 studies report no safety information.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	As of 7/16/15, there is one reported death; a complete report will be forthcoming. This

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					is not part of the presently submitted application.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The applicant requested a partial waiver for patients <12 and a waiver for patients 12-17, based on data from one study which included 322 subjects <17 years old.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	29/46 studies are US data, 17 are based on foreign data.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	NDA relies upon published studies; datasets were not provided.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
37.	Are all datasets to support the critical safety analyses available and complete?			x	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	NDA relies upon published studies; CRFs were not provided.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an			x	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There is one review issue which will need to be addressed.
 The proposed label contains information from the original studies and not from the studies supporting the new dosing regimen and the other proposed changes (e.g., including healthcare providers prescribing Mifeprex and home use of misoprostol). The Sponsor will need to update the proposed label.

<div style="background-color: #cccccc; width: 100%; height: 1.2em; display: flex; justify-content: flex-end; align-items: center; padding-right: 5px;">(b) (6)</div>	7/16/15
Reviewing Medical Officers	Date
<div style="background-color: #cccccc; width: 100%; height: 1.2em; display: flex; justify-content: flex-end; align-items: center; padding-right: 5px;">(b) (6)</div>	7/16/15
	Date

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/s/

(b) (6)
07/16/2015

(b) (6)
07/17/2015

(b) (6)
07/17/2015

EXHIBIT B

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.

PRESCRIBER AGREEMENT FORM

Mifeprex[®] (Mifepristone)
Tablets, 200 mg

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.



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

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

03/2016

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.



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.

PATIENT AGREEMENT FORM



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.

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 C

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)

-----**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

-----**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)

FULL PRESCRIBING INFORMATION: CONTENTS*

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*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.

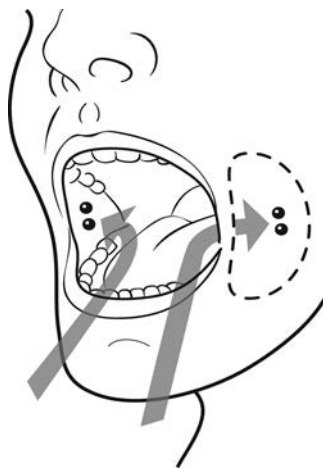
Remove any intrauterine device (“IUD”) before treatment with MIFEPREX begins [see *Contraindications (4)*].

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 antiprogesterone activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities 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.

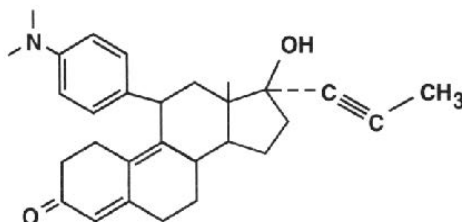
10 OVERDOSAGE

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 antiprogesterational 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 11 β -[p-(Dimethylamino)phenyl]-17 β -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C₂₉H₃₅NO₂. 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-progesterational 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 adrenocorticotrophic 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 C_{max} 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 C_{max} 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 11 β ; 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 pombe* 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 to 14 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 to 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 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

EXHIBIT D

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020687Orig1s020

Trade Name: Mifeprex Tablets

Generic Name: mifepristone

Sponsor: Danco Laboratories, LLC

Approval Date: March 29, 2016

Indication: For use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS

CENTER FOR DRUG EVALUATION AND RESEARCH**020687Orig1s020****CONTENTS****Reviews / Information Included in this NDA Review.**

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	X
Summary Review	X
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	X
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology / Virology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s020

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-020

SUPPLEMENT APPROVAL

Danco Laboratories, LLC

(b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

NDA 020687/S-020
Page 2

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the [REDACTED] (b) (6) and the [REDACTED] (b) (6) [REDACTED] we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

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Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

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

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call [REDACTED] (b) (6)

Sincerely,

{See appended electronic signature page}

[REDACTED] (b) (6)
Center for Drug Evaluation and Research

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ENCLOSURES:

Content of Labeling
REMS

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 E

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s020

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review
 NDA 20-687 S-020 Danco Mifeprex
 3/29/16 FINAL

Cross-Discipline Team Leader Review

Date	March 29, 2016
From	(b) (6)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	20-687
Applicant	Danco Laboratories, LLC
Date of Submission	May 28, 2015
PDUFA Goal Date	March 29, 2016
Proprietary Name / Established (USAN) names	Mifeprex Mifepristone
Dosage forms / Strength	200 mg oral tablet
Proposed Indication(s)	“Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.”
Recommended:	<i>Approval</i>

1. Introduction

Mifeprex was approved for medical termination of pregnancy through 49 days’ gestation on September 28, 2000, under Subpart H (21 CFR 314.520). This subpart provides for approval with restrictions that are needed to assure the safe use of a drug product shown to be safe and effective in treating a serious or life-threatening condition. The approved dosing regimen was 600 mg Mifeprex taken orally followed in two days by 400 mcg misoprostol taken orally. Mifeprex was approved with a restricted distribution plan that included a requirement that Mifeprex be provided only by or under the supervision of a physician who met certain qualifications, including the ability to date pregnancy, to identify an ectopic pregnancy, and to provide (directly or through other qualified physicians) surgical intervention in cases of incomplete abortion or severe bleeding.

The approved regimen and various alternative regimens have been studied widely, and for some years, actual US clinical practice has relied upon different doses of Mifeprex and misoprostol – i.e., 200 mg Mifeprex followed by 800 mcg misoprostol. For a time, misoprostol was primarily administered by the vaginal route; however, the occurrence of rare but lethal infections with *Clostridium sordellii* led to a change to buccal administration of misoprostol (major providers, like the Planned Parenthood Foundation of America [PPFA] also began screening for sexually transmitted infections and providing routine antibiotic prophylaxis before medical abortion). FDA has no evidence that the vaginal use of misoprostol causes infection, and no causal association has been identified between the cases of sepsis and vaginal administration of misoprostol. While labeling was revised to recommend that providers have a high index of suspicion in order to rule out serious infection and sepsis, the Agency did not consider there was sufficient evidence to justify recommending prophylactic antibiotics.

This application seeks revisions to specify use of different dose and a revised dosing regimen (200 mg Mifeprex, followed in 24-48 hours by 800 mcg buccal misoprostol), and to increase the gestational age to which Mifeprex may be used to 70 days. These and other changes

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requested by the Applicant are discussed in detail in Section 7.1. The Applicant's proposed changes also entail revisions to the current Risk Evaluation and Mitigation Strategy (REMS). Based on reconsideration of the need for all elements of the REMS to ensure safe use of Mifeprex, as well as on changes in FDA current practice to standardize REMS programs and materials, FDA has proposed further modifications to the REMS as well (discussed further in Sections 6.1 and 8.6.1).

2. Background

2.1 DESCRIPTION OF PRODUCT

Mifepristone is a progestin antagonist, which competitively blocks the progesterone receptor and increases the uterine sensitivity to prostaglandins. Mifeprex is used with misoprostol, a prostaglandin analog, which has uterotonic action. As the action of mifepristone increases over 24-48 hours, misoprostol is typically administered after an interval no shorter than 24 hours.

2.2 REGULATORY HISTORY

The initial approval of Mifeprex in September 2000 was based upon an application initially submitted by the then-Applicant, the Population Council in 1996. The drug was licensed to Danco Laboratories, LLC to manufacture and market in the US. The application was transferred to the current Applicant, Danco, in October 2002.

The approval came in the third review cycle, after the Applicant addressed CMC, clinical (distribution system), biopharmaceutics and labeling deficiencies satisfactorily. Mifeprex was approved under Subpart H (21 CFR 314.520), with the following restrictions on drug distribution:

“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 other qualified physicians, 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™.
- Must provide each patient with a Medication Guide and 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 both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.

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- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns and other matters.”

In 2007, with the passage of the FDA Amendments Act, Mifeprex was included on the list of products deemed to have in effect an approved REMS under Section 505-1 of the Federal Food, Drug, and Cosmetic Act. A formal REMS proposal was submitted by the Applicant and approved on June 8, 2011 with a Medication Guide, Elements to Assure Safe Use (ETASU), implementation system and timetable for submission of assessments. The REMS is discussed further in Section 8.6.1.

A preNDA meeting was held in January 2015 to discuss the current efficacy supplement. The Division agreed that use of published literature, under a 505(b)(2) approach, could be an appropriate way to support an efficacy supplement to make the desired changes (outlined in Section 7.1). The Division requested safety and efficacy data stratified by gestational age to support the extension of the gestational age through 70 days; the Applicant noted that safety data are not always presented in this manner. Regarding the change in what type of provider could order and dispense Mifeprex, the Applicant noted that state laws govern who is allowed to prescribe in each state. Using a more general term, like “(b) (4) (b) (4)” would avoid specifying a particular type of practitioner. The Division stated that it would discuss this issue further internally and during the review cycle. Regarding the Pediatric Research Equity Act (PREA), the Applicant agreed it would apply to this efficacy supplement; the Applicant was advised to be familiar with language in PREA regarding extrapolation.

2.3 PRIMARY MEDICAL REVIEWERS' RECOMMENDATION FOR APPROVABILITY

The primary reviewers, (b) (6), stated in their joint review dated March 29, 2016:

The clinical reviewers recommend an approval action on this efficacy supplement.

(b) (6) did not recommend any postmarketing requirements or commitments.

Team Leader Comment:

I concur with (b) (6) recommendations.

3. CMC

No new CMC information was submitted in the efficacy supplement. (b) (6) reviewed the PLR conversion of the label. Her review, dated January 11, 2016 states the following:

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“No changes have been made in the approved chemistry, manufacturing and controls. The approved 200 mg tablet will be used. This review evaluates the PLR conversion of the labeling. Sections 3, 11, and 16 of the PLR labeling, and the Highlights of Prescribing Information, have been evaluated from a chemistry perspective.

Overall Evaluation: Acceptable. The labeling provided in Section 3, Section 11, and Section 16, and the Highlights of Prescribing Information, is identical in content to the approved information. The PLR conversion labeling, therefore, is acceptable from a chemistry perspective. The PLR label also corresponds to the content and format required in 21 CFR 201.57.

During the review cycle, the Applicant submitted a chemistry, manufacturing and controls supplement (021) that provided for a new manufacturing site for the finished product, and for revised product packaging, such that the product will be provided as a single tablet packaged in the approved blister card, rather than the currently approved presentation of three tablets per blister card. The supplement was approved on March 10, 2016. Subsequently, the Applicant revised the labeling submitted to the efficacy supplement to reflect the new packaging information. (b) (6) re-evaluated the proposed labeling following this revision and concluded that it was acceptable in her second review of Supplement 020, dated March 21, 2016.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted by the Applicant. The pharmacology/toxicology review was limited to labeling; the primary Toxicology Reviewer, (b) (6) reviewed and made labeling comments on Sections 8, 12, and 13, which were conveyed to the Applicant.

(b) (6) made the following recommendation in his review dated March 4, 2016:

Conclusion: This supplement is approvable from a Pharm/Tox standpoint.

5. Clinical Pharmacology/Biopharmaceutics

5.1 CLINICAL PHARMACOLOGY REVIEW

The Applicant did not conduct any new clinical pharmacology studies pertaining to the new dosing regimen, but provided literature and one study report by (b) (4) relating to the pharmacokinetics (PK) of misoprostol following various routes of administration. The PK of the 200 mg Mifeprax tablet has not been characterized in women, but data are available based on men and were submitted in the original NDA. The primary Clinical Pharmacology Reviewer, (b) (6) has determined that these data are appropriate for inclusion in labeling.

No drug-drug interaction studies were conducted, but (b) (6) noted that CYP3A4 inducers may have a significant effect on mifepristone PK. Because the lowest effective dose of mifepristone for medical abortion has not been determined, and because misoprostol contributes to the treatment efficacy, the impact of CYP3A4 inducers on clinical efficacy is unknown. It does not appear that misoprostol concentrations are impacted by CYP3A4 inducers.

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(b) (6) stated the following in his review dated March 29, 2016:

The (b) (6) (b) (6) has reviewed the available clinical pharmacology information in relation to the newly proposed regimen for Mifeprex®. We find the application to be acceptable from a Clinical Pharmacology perspective. An agreement on the language in the package insert is reached between the Sponsor and the Division on March 29, 2016 and there are no pending issues from the (b) (6).

No post-marketing commitments or requirements were recommended.

5.2 PK AND PHARMACODYNAMICS OF DIFFERENT ROUTES OF ADMINISTRATION FOR MISOPROSTOL

Because some of the studies submitted by the Applicant in support of this efficacy supplement utilized misoprostol given by other routes of administration, I reviewed several publications on the PK associated with various routes of misoprostol administration in order to determine whether it is relevant to consider these studies as supportive, despite use of different routes of administration for misoprostol.

Two articles relating to the serum concentrations and pharmacodynamic (PD) effects of various routes of misoprostol administration were reviewed. Meckstroth 2006¹ evaluated PK and uterine response for five hours after randomizing 40 women seeking first trimester pregnancy termination to various routes of epithelial administration (rectal, buccal, dry tablets vaginally and moistened tablets vaginally). There was considerable inter-subject variability in PK for all routes of administration, although variability was non-significantly less in the buccal arm. Serum levels after both vaginal routes were much higher than for the buccal route of administration, but the uterine activity was very similar. Although no difference in adverse events between arms was noted, the study was not sufficiently powered for this outcome.

Schaff 2005² compared PK of buccal and sublingual administration of misoprostol and reported higher systemic levels and more frequent adverse events with sublingual administration. Uterine response was not directly evaluated in this study.

A randomized clinical trial by Middleton 2005³ compared treatment regimens comprising 200 mg mifepristone with 800 mcg misoprostol 1-2 days later, taken either vaginally or buccally, in 442 women with gestations through 56 days. The difference in success, defined as a complete abortion without surgical intervention, was not statistically significantly different by misoprostol route of administration (buccal: 95%, vaginal 93%). The rate of ongoing pregnancy was higher for the vaginal route (1.9% vs. 0.9% for buccal); the significance of this difference was not reported.

¹ Meckstroth KR et al. Misoprostol administered by epithelial routes. *Obstet Gynecol* 2006; 108: 582-90

² Schaff EA, DiCenzo R, and Fielding SL. Comparison of misoprostol plasma concentrations following buccal and sublingual administration. *Contraception* 2005; 71: 22-5

³ Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005; 72: 328-32

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Team Leader Comment:

The PD data are supportive of the relevance of studies utilizing the vaginal route of administration to consideration of the proposed dosing regimen. Despite different PK profiles, it appears that the treatment effect of vaginal and buccal misoprostol is likely to be similar. Data on sublingual administration may be less generalizable due to the higher PK and adverse event frequency compared to buccal administration.

6. Consultative Reviews

6.1

(b) (6) provided recommendations to (b) (6) based on its review of the proposed modifications to the REMS. In the (b) (6) review dated March 29, 2016, the primary reviewer, (b) (6) indicated (b) (6) agreement with the following Applicant-proposed changes:

- Removal of the term “under Federal law” from the Prescriber’s Agreement
- Replacement of the word “physician” with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex; (b) (6) believes that the Applicant’s proposed terminology of “(b) (6) (u) (4)” is too broad and that a more appropriate description is “healthcare provider who prescribes.”

In the course of this review, input was obtained from the (b) (6) (b) (6) and (b) (6) and (b) (6) considered the recent REMS Assessment data submitted by the Applicant in June 2015, postmarketing summary reporting by the (b) (6) (b) (6) safety data obtained over the past 16 years, and information about current clinical practice. Based on the information reviewed, as well as current FDA thinking about REMS language and organization, (b) (6) and (b) (6) considered the ongoing need for each REMS element to ensure that the benefits outweighed the risks of Mifeprex and proposed additional modifications to the REMS, including:

- Removal of the Medication Guide from the REMS. While the Medication Guide remains an important tool for patient education, and will still be distributed to each patient as part of labeling, it is not a necessary element of the REMS to ensure that the benefits outweighed the risks of Mifeprex
- Modification of Element to Assure Safe Use (ETASU) A, i.e., the Prescriber’s Agreement. (b) (6) recommends changing the name of the document to the Prescriber’s Agreement Form to be consistent with terminology used in other REMS programs. The gestational age at which Mifeprex may be used should be modified in accord with revised labeling in the Prescribing Information. References to “physician” should be changed to “healthcare provider who prescribes.”
- Modification of ETASU D, i.e., the Patient’s Agreement. (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
 - The established safety profile over 15 years of experience with Mifeprex is well-characterized and known serious risks occur rarely
 - The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208

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- The current Patient Agreement is duplicative of established clinical practice, which provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment
- Other revisions to the REMS document are recommended for consistency with changes described above and to reflect current FDA thinking and practice regarding language and flow in REMS documents. These include modification of the Mifeprex REMS goal, changes in requirements to certify prescribers (removal of the requirement to obtain a Patient Agreement and other minor edits).
- Modification of the REMS goals. With the recommendation for removal of the Patient Agreement, the goals statement should be revised 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.

A full description of the (b) (6) recommendations is included in the review dated March 29, 2016. The overall (b) (6) recommendation stated:

(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.

Team Leader Comment:

I concur with all of (b) (6) recommendations; Section 8.6.1 further discusses my recommendations with regard to the REMS.

7. Clinical

7.1 OVERVIEW OF CLINICAL PROGRAM

This efficacy supplement is supported entirely by data from the published literature; no clinical trials were conducted specifically in support of the supplement. It is notable that many of the evidence-based changes proposed are reflective of how Mifeprex is actually administered in current US clinical practice. Thus, many of the studies are observational in nature, and report on the outcome of current practice.

The following are the changes requested by the Applicant:

1. Change in dose regimen (b) (4)
 - a. Mifeprex dose decreased from 600 mg to 200 mg, taken orally on Day 1
 - b. Misoprostol dose increased from 400 mcg to 800 mcg taken, and route of administration changed from oral to buccal
 - c. Interval between Mifeprex dose and misoprostol dose administration and acceptable location for misoprostol administration changed; from two days (currently labeled to take misoprostol in the office on Day 3) to 24-48 hours; misoprostol to be dispensed on Day 1 to be taken 24-48 hours later at home (or other location appropriate for the patient)

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The studies reviewed in the succeeding sections include the proposed regimen where noted, while some studies are based on regimens that vary from that proposed (e.g., vaginal misoprostol, lower misoprostol dose). As discussed in Section 5.2, PK, PD and clinical data indicate the relevance, particularly of data on vaginally-administered misoprostol. Unless specifically noted, the definition of success for the treatment regimen is defined as complete expulsion of the pregnancy without need for surgical intervention for any reason. Where the rate of ongoing pregnancy is discussed as an outcome measure, this refers to identification of an ongoing pregnancy during follow-up, typically by ultrasound.

7.2 CHANGE IN DOSING REGIMEN

In general, studies of treatment regimens evaluated specified regimens of mifepristone and misoprostol (i.e., they did not study varying doses and routes of administration as individual elements). For this reason, the review will discuss studies that support the proposed revised doses of Mifeprex and misoprostol and the buccal route of administration of misoprostol as a single topic. Some studies did specifically evaluate the dosing interval between mifepristone and misoprostol or the home administration of misoprostol, so these studies are discussed as separate topics.

7.2.1 Revised dose for Mifeprex and revised dose and route of administration for misoprostol

There is a substantial body of literature supporting the proposed dosing regimen, which includes a lower dose of Mifeprex and a higher dose of misoprostol compared to the currently labeled regimen, and a change from oral to buccal administration of misoprostol.

Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff 2012⁴, Boersma⁵, Sanhueza Smith⁶) and one randomized controlled trial (RCT) (Olavarrieta⁷) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin⁸ covered 20 studies, all but one of which used the proposed regimen in gestations through 70 days (the remaining study used 400 mcg of buccal misoprostol). For those publications that provided overall success rates, these were in the range of 97-98%. Many of these papers also provided success rates stratified by week of

⁴ Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

⁵ Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011; 16: 61-6

⁶ Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015; 22: 75-82

⁷ Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousiequez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. *Bull World Health Organ* 2015; 93: 249-258

⁸ Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion *Obstet Gynecol: a Systematic Review*. *Obstet Gynecol* 2015; 126(1): 12-21

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gestation; these are discussed in Section 7.3. The large systematic review⁸ of over 33,000 women through 70 days gestation provided information on rates of serious adverse events and reported rates of infection ranging from 0.01-0.5%, transfusion from 0.03-0.6% and hospitalization from 0.04-0.9% (see Section 8.1).

A number of additional studies assessed the proposed regimen through 63 days gestation, overall success rates ranged from 91-99.6%, with most in the 96-97% range. A few studies included only earlier gestational ages, e.g., through 56-59 days, and reported success rates from 92-98%, with ongoing pregnancy rates under 1%. Again, many of these papers provide success rates stratified by week of gestation, which are shown in Table 4 under the heading "Increased Gestational Age." Safety findings from this group of publications included a finding that fever/chills were more frequent with buccal vs. oral misoprostol (Winikoff 2008⁹) and a similar finding of higher non-serious adverse events (e.g., vomiting, fever/chills) for the 800 mcg vs. a 400 mcg dose of misoprostol (Chong 2012¹⁰), while Middleton³ reported similar rates of common adverse events for buccal and vaginal misoprostol, with the exception of diarrhea, which was higher in women receiving misoprostol buccally. Raymond's systematic review¹¹ of global studies included over 45,500 women, of whom 2,200 received misoprostol doses \geq 800 mcg, and reported rates of hospitalization of 0.3% and of transfusion of 0.1% in the population overall. The large US observational study (Gatter¹²) of over 13,000 women through 63 days gestation reported rates of infection that required hospitalization of 0.01%, and transfusion of 0.03%, while a large Australian observational study (Goldstone 2012¹³) reported rates of known/suspected infection of 0.23%, and of hemorrhage of 0.1%. Finally, a study (Ireland¹⁴) that compared over 30,000 women undergoing medical vs. surgical abortion through 63 days reported non-significantly different rates of a composite outcome including hospitalization, emergency department visit, infection and transfusion, with a total rate over the entire population of 0.1%.

Other relevant publications include the systematic review by Raymond¹¹ of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of

⁹ Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008; 112(6): 1303-1310

¹⁰ Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. *Contraception* 2012; 86: 251-256

¹¹ Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

¹² Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91: 269-273

¹³ Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. *Med J Austral* 2012; 197: 282-6

¹⁴ Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. *Obstet Gynecol* 2015; 126: 22-8

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mifepristone. Assessing the efficacy by misoprostol dose, the paper noted that doses ≥ 800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%. The paper by Kulier¹⁵ presents a Cochrane systematic review of 58 studies comparing different doses of mifepristone and misoprostol, which concluded that the 200 mg dose of mifepristone is as effective as the 600 mg dose, and that oral misoprostol is less effective than vaginal misoprostol, while buccal is as effective as vaginal but has a higher frequency of adverse events. Raghavan¹⁶ used a 400 mcg dose of buccal misoprostol along with 200 mg mifepristone and reported a success rate of 97.1%.

Data for all relevant studies are provided in Table 4.

Team Leader Comments:

- **The available data support the safety and efficacy of the new proposed dosing regimen, including the revised doses of Mifeprex and misoprostol and the buccal route of administration for misoprostol.**

- ([REDACTED] (b) (4)

However, there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing this regimen from labeling.

7.2.2 Revised time and location for misoprostol dosing

Dosing Interval

The interval between the dose of Mifeprex and the misoprostol administration is currently described as two days; the supplement proposes to modify this to “24 to 48 hours.” Allowing for a broader range in the dosing interval gives the woman more flexibility, and may shorten the time to complete abortion, since this usually follows fairly rapidly after misoprostol administration (see Section 7.6).

Studies supporting the new dosing regimen described in the preceding section used the proposed dosing interval unless otherwise specified. In addition, data specifically supporting the new interval were provided in a review article by Wedisinghe¹⁷, which identified five RCTs, four of which used the proposed dose (Creinin 2004¹⁸, Creinin 2007¹⁹, Guest 2007²⁰

¹⁵ Kulier R, Kapp N, et al. Medical methods for first trimester abortion (Review). The Cochrane Library 2011, Issue 11: 1-126

¹⁶ Raghavan S, et al. Comparison of 400 mcg buccal and 400 mcg sublingual misoprostol after mifepristone medical abortion through 63 days' LMP: a randomized controlled trial. Contraception 2010; 82: 513-9

¹⁷ Wedisinghe L and Elsandabese D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. Contraception 2010; 81(4): 269-74. doi: 10.1016/j.contraception.2009.09.007. Epub Oct 29, 2009

¹⁸ Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859

¹⁹ Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, and Meyn LA. Medical Abortion at the Same Time (MAST Study Trial Group). Mifepristone and misoprostol administered

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and Schaff 2000²¹), although in all four, the misoprostol was administered vaginally. Three of the studies included gestations through 63 days; Schaff included gestations through 56 days. Intervals compared included simultaneous administration of misoprostol after Mifeprax vs. 24 hour interval, 6 hours vs. 36-48 hours, 6-8 hours vs. 23-25 hours, and 1 day vs. 2 days vs. 3 days. Rates of successful terminations were equivalent based on statistical tests of non-inferiority. A meta-analysis of all five studies found a non-significant odds ratio for failure for shorter vs. longer dosing intervals, but a trend for lower success if a dosing interval < 8 hours is used. Safety data were not reported in this review.

Chen & Creinin's systematic review⁸ of 20 studies including over 33,000 women, all but one using the proposed regimen, compared the success of dosing intervals of 24 hours with intervals ranging from 24-48 hours. The success rate in six studies that used a 24-hour interval through 63 days gestation was 94.2%, compared to the rate of 96.8% in 14 studies that used a 24-48 hour interval, and this difference was statistically significant. The difference remained statistically significant, with greater success for the 24-48 hour dosing interval, when the data were stratified by gestational age (≤ 49 days and 50-63 days). However, the overall rate of ongoing pregnancies did not differ significantly by dosing interval. Safety data were summarized in this review, but not discussed with respect to dosing interval.

Team Leader Comment:

The proposed dosing interval allows for earlier administration and an expanded window over which misoprostol may be taken, while maintaining the originally labeled timing for misoprostol administration as the upper limit of the interval. The available data support that the efficacy of the treatment regimen is not compromised by revising the dosing interval to 24-48 hours.

Home Administration of Misoprostol

In the review cycles for the original approval of Mifeprax, FDA originally considered allowing the option of taking misoprostol either at home or at the prescriber's office; however, re-review of the data provided at that time led to the determination that the data did not provide substantial evidence of safety and efficacy for home administration. Nonetheless, in current clinical practice, it is common to provide the woman with misoprostol (or a prescription for misoprostol) at her initial appointment (at which the Mifeprax is administered) and allow her to take it at home at the appropriate time. In this submission, the Applicant has submitted additional data in support of administration of misoprostol at a location convenient to the woman. While no studies specifically evaluated treatment outcomes for home vs. clinic dosing of misoprostol, the studies listed in Table 4 under the heading "Home Dosing of Misoprostol" all included home dosing of a mifepristone

simultaneously versus 24 hours apart for abortion a randomized controlled trial. *Obstet Gynecol* 2007; 109: 885-894

²⁰ Guest J, Chien PF, Thomson MA and Kosseim ML. Randomized controlled trial comparing the efficacy of same-day administration of mifepristone and misoprostol for termination of pregnancy with the standard 36 to 48 hour protocol. *BJOG* 2007; 114: 207-15

²¹ Schaff EA, Fielding SL, Westhoff C et al. Vaginal misoprostol administered 1, 2 or 3 days after mifepristone for early medical abortion: A randomized trial. *JAMA* 2000; 284: 1948-53

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and misoprostol dosing regimen as part of the treatment regimen. One study and one literature review included women with gestations through 70 days. The majority of the studies used the proposed regimen; a few used vaginal misoprostol, which is considered relevant for reasons previously discussed.

The Raymond systematic review¹¹ of 87 studies with over 45,000 women included a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration and dosing intervals used in gestations through 63 days. Roughly half of the studies included in this review did not require women to take misoprostol in-clinic. Rates of treatment failure and of ongoing pregnancy were very similar regardless of whether misoprostol was taken in-clinic or at another location. A logistic regression analysis of factors leading to increased failure found no evidence that home use of misoprostol increased rates of treatment failure rates or serious complications.

Therefore, the efficacy and safety data provided in those studies support the proposal that misoprostol does not need to be restricted to in-clinic administration to provide a safe and effective medical abortion using the proposed dosing regimen. Given the rapid onset of bleeding and cramping after taking misoprostol, allowing home administration increases the likelihood that the woman will be in an appropriate location when the process begins.

Team Leader Comment:

The available data support the safety and efficacy of the proposed treatment regimen, regardless of the location in which misoprostol is taken.

7.2.3 Option for an additional misoprostol dose

Although Reeves²² reports that fewer than 5% of women taking Mifeprax and vaginal misoprostol will have a persistent gestational sac one week after using Mifeprax, it is important to know whether all such cases require surgical intervention, or whether a second dose of misoprostol may result in a complete abortion. The Reeves²² publication pooled data from two RCTs (Creinin 2004¹⁸ and 2007¹⁹) in which women who had not expelled the gestational sac per a sonographic assessment 6-11 days after taking Mifeprax received a second vaginal dose of misoprostol. Of 68 women with persistent gestational sac, 62% had a complete abortion per a follow-up ultrasound one week after the second dose of misoprostol. Of 14 women who had an ongoing pregnancy (as determined by fetal cardiac activity at initial follow-up), 63% no longer showed fetal cardiac activity following the second dose.

A number of other studies included the option for a second dose of misoprostol as part of the evaluated treatment regimen. Indications for an additional dose include no bleeding within a specified time after the first misoprostol dose or a finding of an incomplete abortion at follow-up. Studies that specifically report the success rate of a repeat dose of misoprostol are:

- Winikoff 201²⁴ – studied the proposed regimen through 70 days gestation; of the few women who received a second dose for an incomplete abortion at follow-up, the success rate was 91% at 57-63 days and 67% at 64-70 days.

²² Reeves MF, Kudva A and Creinin M. Medical abortion outcomes after a second dose of misoprostol for persistent gestational sac. *Contraception* 2008; 78: 332-5

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- Chen and Creinin 2015⁸ – a systematic review of 20 studies, all but one of which used the proposed regimen up through 70 days; success of a second dose ranged from 91-100%
- Boersma 2015⁵ – included pregnancies through 70 days treated with the proposed regimen; five of 330 women took a second dose due to absence of bleeding 48 hours after first dose; the success rate was 80%
- Louie 2014²³ – studied the proposed regimen to 63 days; in 16 women (of 863) who took a second dose of misoprostol, the success rate was 100%
- Chong 2012¹⁰ – compared the proposed regimen to a lower dose of misoprostol; the success of a second dose of misoprostol was 92% overall, but the number of women in each dose arm getting a second dose was not specified.
- Winikoff 2008⁹ – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%

Three other studies (Bracken 2014²⁴, Coyaji 2007²⁵, and Raghavan 2011¹⁶) are less relevant because they evaluated a 400 mcg dose of misoprostol, but these studies still reported high success rates for a second dose. In Bracken, gestational-age stratified success rates after a second dose were 90.9% for gestations from 57-63 days and 86.3% from 64-70 days among the 6-11% of women who took a second dose; in Raghavan, they were 97% for gestations of ≤ 49 days and 100% for gestations of 50-63 days; and Coyaji reported 86% success overall.

Safety reporting over all of these studies did not specifically address safety findings in the subset of women who received a second dose, but there were no unexpected safety findings overall. The Gallo 2006²⁶ systematic review of studies that included more than one dose of misoprostol (varying dosing regimens) provided further safety data that are discussed in the primary review.

Team Leader Comments:

- **A finding of an incomplete abortion could indicate an ongoing pregnancy or that the pregnancy has been terminated but that the woman has not yet fully expelled the products of conception. The Applicant indicates that only about 1-5% of women will need a second dose of misoprostol following the initial Mifeprex treatment regimen.**
- **The available data support the safety and efficacy of a repeat dose of misoprostol if complete expulsion of the products of conception has not occurred but the pregnancy**

²³ Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. *Eur J Contracept Reprod Health Care* 2014; 19(6): 457-464

²⁴ Bracken H, Dabash R, Tsertsvadze G et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. *Contraception* 2014; 89(3): 181-6

²⁵ Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? *BJOG* 2007; 114: 271-278

²⁶ Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. *Contraception* 2006; 74: 36-41

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is not ongoing. The relatively high success rates after a second dose indicate that this option is likely to reduce the need for a surgical intervention. While there is a suggestion that the success rate following a second dose of misoprostol may be somewhat lower at more advanced gestational ages, there is no evidence that the practice of offering an additional dose results in adverse effects.

- **Surgical evacuation of the uterus is still recommended in labeling in the case of an ongoing pregnancy.**
- **The labeling will not specify how follow-up will be performed; that will be a decision made between the healthcare provider and patient. Based on the results of a number of studies that evaluated the utility of symptom questionnaires and home pregnancy tests, the healthcare provider and patient can safely determine if it is likely that she has not had a complete abortion. Current professional guidance (American College of Obstetricians and Gynecologists Practice Bulletin 143²⁷) provides recommendations on making this determination. In the case where it is determined that an incomplete abortion is likely, the patient would come in for a visit and discuss options, including a second dose of misoprostol if the pregnancy has been terminated but she has not completely expelled all products. As noted, in the case of an ongoing pregnancy, surgical termination is recommended.**

7.3 CHANGE IN GESTATIONAL AGE

The Applicant submitted four studies through 70 days gestation using the proposed regimen, one of which was in the US, for a total of 2,994 women \leq 70 days. Also relevant is a global systematic review of 20 studies, all but one using the proposed regimen. Three of the studies also allowed for a repeat dose of misoprostol if needed.

- In the three studies (Winikoff 2012⁴, Boersma⁵, Sanhueza Smith⁶) evaluating efficacy by gestational age, rates for 64-70 days were 91.2, 92.8 and 96.2%, respectively.
- The fourth study (Olavieretta⁷) used the proposed regimen to determine efficacy when non-physician providers were used; efficacy through 70 days was 98.4% with physician providers and 97.9% with nurse providers.
- The systematic review (Chen and Creinin⁸) provided a pooled success rate for 64-70 days of 93.1%; a total of 33,846 women were \leq 70 days.
- Another systematic review (Abbas²⁸) of various regimens included an arm with the proposed regimen, with a rate at 64-70 days of 92.5% in that arm.

There are two more studies through 70 days that used regimens that deviated from that proposed but are relevant because these doses and routes of administration are expected to have similar or lower effectiveness.

- One (Gouk²⁹) used 800 mcg vaginal misoprostol; the success rate was 94.5% at 64-70 days

²⁷ American College of Obstetricians and Gynecologists. Practice bulletin No. 143: medical management of first-trimester abortion. *Obstet Gynecol* 2014; 123(3): 676-92. doi:10.1097/01.AOG.0000444454.67279.7d.

²⁸ Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70 days gestation. *Contraception* 2015; 92: 197-9

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- One (Bracken²⁴) used 400 mcg sublingual misoprostol; the success rate was 91.9% at 64-70 days; although this is a lower dose than proposed, the PK concentrations of misoprostol are higher after sublingual dosing², so it is difficult to determine if the efficacy reported in this study is generalizable to the proposed regimen

Therefore, overall, the efficacy at 64-70 days appears to be in the range of 91-98% for the proposed regimen.

While not all studies thoroughly discussed adverse events, those that reported did not have unexpected rates of serious or common adverse events (see additional discussion of safety in Section 7.2.1).

Additional studies included women at gestational ages greater than the currently approved 49 days but < 64 days; these are listed in Table 4 under the heading “Increased Gestational Age.”

Team Leader Comments:

- **The available data support the safety and efficacy the proposed regimen for use in gestations through 70 days.**

7.4 CHANGE IN FOLLOW-UP

Current Mifeprex labeling states that “Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex.” The Applicant proposes that a more flexible follow-up regimen is safe and effective; proposed labeling would state “Patients should follow-up with their healthcare provider approximately 7-14 days after the administration of Mifeprex.”

The impact of the timing of follow-up was assessed in Raymond’s systematic review¹¹ of studies using various treatment regimens through 63 days gestation. While some have posited that earlier follow-up may result in a higher rate of surgical intervention (for women who would have had complete expulsion had they been given a bit more time), Raymond’s analyses found no difference in failure rates for women followed < one week after Mifeprex vs. a week or more after Mifeprex.

The primary reviewers discussed the extensive data on various follow-up options that may be used to identify those women who warrant further evaluation and possibly further intervention. Studies in Table 4 under the “Method of Follow-up” were considered, and include a variety of study designs and regimens through 63 days gestation. For this topic, the specific regimen studied is less important, because there is no reason to presume that a particular follow-up strategy would be differentially accurate for different treatment regimens. Overall, it appears that various methods of follow-up, including home pregnancy testing and phone contact during which the patient is queried about symptoms (bleeding, etc.), are acceptable alternatives to in-clinic follow-up.

²⁹ Gouk EV et al. Medical termination of pregnancy at 63-83 days gestation. British J Obstet Gyn 1999; 106: 535-539

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Team Leader Comments:

- **The Raymond analysis¹¹ of 87 trials finding no difference in failure rates for earlier (< one week) vs. later (≥ one week) follow-up supports the broadened window proposed for follow-up.**
- **The available data support the proposal that there are a variety of follow-up modalities that can adequately identify the need for additional intervention, not all of which require in-clinic assessment of the patient.**
- **The labeling will not be directive regarding specific details of how follow-up will be performed; that will be a decision made between the healthcare provider and patient.**

7.5 CHANGE IN PROVIDER

The current labeling states that Mifeprex “should be prescribed only by physicians” and the Prescriber’s Agreement in the REMS specifies that “...Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications...” In addition, current labeling states that Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber’s Agreement. However, labeling states that other healthcare providers, acting under the supervision of a qualified physician, may also dispense/administer Mifeprex to patients. The Applicant now proposes changes to the labeling and REMS to permit other healthcare providers, such as nurse practitioners, certified nurse midwives, and physician assistants, to order, prescribe, dispense, and administer Mifeprex. The language proposed by the Applicant for this broadened category of providers was “(b) (4)”. The data supporting such a change are discussed here.

Three RCTs (Olavarrieta 2015⁷, Kopp Kallner 2015³⁰ and Warriner 2011³¹) and one comparative study (Puri 2015³²) addressed the safety and efficacy of medical abortion when performed by non-physician healthcare providers. All used the proposed dosing regimen, except Warriner, who studied vaginal misoprostol. Almost 1,500 women (over 700 of whom had non-physician care) had gestations through 70 days or more, while the Kopp Kallner and Warriner studies include almost 2,300 women (over 1,000 of whom had non-physician care) with gestations up to 63 days. Success rates are ≥ 96%, regardless of gestational age, and very similar across provider types, and across all studies, the single report of serious adverse events concerned a physician-treated woman who was hospitalized for bleeding (Olavarrieta⁷).

³⁰ Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomized controlled equivalence trial. BJOG 2015; 122: 510-517

³¹ Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61

The Warriner study is described in the Renner 2013 systematic review discussed in the primary review; because this is the only study in that systematic review that evaluated medical (rather than surgical) abortion, I discuss that study directly here.

³² Puri M, Tamang A, Shrestha P, Joshi D. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. Reproductive Health Matters 2015; Suppl(44): 94-103

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Team Leader Comments:

- The available data support the safety and efficacy of allowing certain non-physician healthcare providers to order, dispense and administer Mifeprax, provided they meet the requirements for certification described in the REMS.
- However, the Division was concerned that the Applicant's proposed terminology (" (b) (4) was non-specific, as there are many types of (b) (4) (b) (4). The Division and (b) (4) propose use of the term "healthcare provider who prescribes." Use of this terminology will include other practitioners who prescribe; in addition, this phrase is consistent with language in the statute. This wording will limit healthcare providers who may become certified under the REMS to those who are licensed in their state to prescribe medications. The specific practitioners to whom this terminology applies will be defined on a state-by-state basis, as state laws regulate prescribing abilities of various healthcare practitioners.

7.6 CHANGE IN TIME TO EXPULSION

The Applicant proposed to change the description in labeling of the time between misoprostol administration and expulsion of the products of conception from "4-24 hours" to "2-24 hours."

Winikoff 2012⁴ provided data using the proposed regimen for gestations at 57-63 days and at 64-70 days demonstrating that by five hours post-misoprostol, about 50-60% of women have expelled the products of conception; expulsion began shortly after dosing and was virtually complete by 24 hours. Women in the earlier gestational age group were more likely to expel sooner (for example, the proportion of women with expulsion at three hours was significantly higher in the 57-63 day group than the 64-70 day group). Other studies (Lohr³³ [which administered misoprostol 5 minutes after Mifeprax], Creinin 2004¹⁸ and 2007¹⁹ [which used vaginal misoprostol]) addressing the time of expulsion did not use the exact proposed regimen, but similarly found that the average onset of cramping was 1.5-2 hours and onset of bleeding was 2-3 hours after misoprostol dosing.

Team Leader Comment:

The available data support the revised statement about the typical time frame for expulsion after misoprostol dosing. Accurate information will help the patient ensure that she is in an appropriate setting when expulsion is likely to occur.

7.7 REGULATORY CHANGES

7.7.1 Addition of Misoprostol to the Indication Statement

The Mifeprax labeling currently states in the indication statement of the Indication and Use (I&U) section:

Mifeprax is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

Reference to misoprostol is made in this section several sentences later, in the statement:

³³ Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD. Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study. *Contraception* 2007; 76: 215-220

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Patients taking Mifeprex must take 400 mcg of misoprostol two days after taking mifepristone unless complete abortion has already been confirmed before that time.

The Applicant proposed to include misoprostol in the actual indication statement, as follows:

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

The other explanatory statements in the I&U section will be moved to other appropriate sections of labeling (e.g., Dosing and Administration, Warnings and Precautions).

Team Leader Comments:

- **I agree with the proposed addition of misoprostol to the indication statement. All of the data reviewed for this supplement and for the original Mifeprex application was based upon a combined regimen of the two drugs. In addition, reference is made throughout labeling to use of misoprostol as part of the combined regimen. Further, this is consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include "Information if drug is to be used only in conjunction with another therapy."**
- **As with other products used concomitantly with another drug that is referenced in the labeling, the Mifeprex labeling will refer the reader to misoprostol labeling for specific information on that drug.**

7.7.2 Removal of "Under Federal law"

This term is used in two places in the Prescriber's Agreement:

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

Under Federal law, each patient must be provided with a Medication Guide.

The Division and (b) (6) researched the origin of this language in the REMS, and neither was able to determine a specific clinical rationale for its inclusion. The phrase appears redundant, because all of the requirements under the REMS are imposed as a matter of Federal law. Per the (b) (6) review, there is no precedent for use of this term in other REMS documents.

Team Leader Comment:

I agree that the term "Under Federal law" should be removed from the Prescriber's Agreement.

8. Safety

As noted earlier, the discussion of particular topics relating to proposed changes in the regimen includes review of both efficacy and safety data. More general safety information is addressed in this section.

Exposure to the proposed regimen, as demonstrated in the literature for various topics, is shown in Table 1. Although supportive data from variants on the proposed regimen was also reviewed, this table refers only to studies evaluating the exact proposed regimen, with the exception of the follow-up topic, because the specific regimen used is not expected to impact the data obtained on the utility of various follow-up methods. In addition, while of considerable value, data from systematic reviews or meta-analyses are not included here because they may result in repeat counting of subjects from individual studies. There are

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additional studies that allowed the option of an additional dose of misoprostol, but only those studies that clearly reported the effectiveness of that second dose are listed here. It should be noted that only a single study provided age-stratified efficacy data that included females under age 18, but a number of studies included pregnant females below the age of 18 in their overall study population.

Table 1 Number of Studies and Subjects by Topic and Region

Topic	US Data # of studies (N)	International Data # of studies (N)
Revision of Dosing Regimen (doses of mifepristone and misoprostol, route of administration for misoprostol, dosing interval)	7 (16,794)	15 (18,425)
Home Use of Misoprostol [^]	3 (1,728)	5 (15,896)
Additional Dose of Misoprostol [*]	2 (34)	4 (21+)
Gestational Age 63-70 days	1 (729)	3 (2,392)
Method of Follow-up	3 (1,709)	7 (6,159)
Time of Follow-up	0	1 (45,528)
Change in Healthcare Provider	0	3 (1,222 with non-MD provider)
Use in Adolescents [#]	1 (322 ≤ 16 years, 283 17 years)	0

[^]Data shown here represent only studies in which success after home use was specifically reported; many other studies included home dosing of misoprostol as part of the treatment regimen

^{*}Data shown in this row represent only the number of subjects for whom efficacy of the second dose was specifically reported; as noted previously, many studies included the option of a second dose, but did not specifically address the number of women who received a repeat dose. Given that about 1-5% of women may be eligible for a receiving a second dose, the number treated with a second dose is likely markedly higher than what is shown here.

[#]This number is based only on the Gatter study¹², which provided age-stratified efficacy data. However, other studies did include females under age 17.

Team Leader Comment:

The volume of evidence supporting each of the proposed changes is acceptable.

8.1 SERIOUS ADVERSE EVENTS

Deaths and Serious Adverse Events

Death in association with abortion is extremely rare. Recent CDC information³⁴ reports a fatality rate for legal abortion (medical and surgical) over 2003 to 2011 to be 0.73 per 100,000 abortions. In the current submission, most articles did not specifically comment on deaths, possibly because this is such a rare outcome. Of seven US studies, only Grossman 2011³⁵ reported on deaths, noting 0 deaths among almost 600 women who received the proposed regimen through 63 days gestation. An additional Australian study (Goldstone

³⁴ http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s_cid=ss6410a1_e.

³⁵ Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;18:96-303

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2012¹³) of the proposed regimen used through 63 days reported a single death among 13,345 medical abortions (0.007%).

While not all studies provided information on serious adverse reactions associated with the Mifeprax regimen, the primary review provides a detailed discussion of reported rates of hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. The latter is not an adverse reaction because an ectopic pregnancy would exist prior to the Mifeprax regimen; it represents instead a failure to diagnose an ectopic pregnancy. Overall rates are as follows:

- Hospitalization: 0.04-0.6% in US studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women
- Serious infection/sepsis: 0-0.2% in US and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in US studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

Upadhyay³⁶ reported a 0.31% rate of major complications (including incomplete or failed abortion, hemorrhage, infection or uterine perforation that required hospitalization, surgery or transfusion) for medical abortions (dosing regimen unspecified) through 63 days; this was about double the rate reported for first trimester aspiration abortions and statistically significantly higher. However, these rates were driven by higher rates of incomplete/failed abortion; rates of hemorrhage (0.14%) and infection (0.23%) did not differ from those associated with aspirations.

Team Leader Comment:

Overall, the rate of deaths and SARs is acceptably low and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen.

8.2 OTHER ADVERSE EVENTS

8.2.1 Common AEs

Examination of the common adverse reaction data by US vs. non-US study location revealed that there were differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the US studies. There is no reason to anticipate regional differences in the safety profile for the same treatment regimen, so these differences likely reflect lower ascertainment or subject reporting of adverse reactions in non-US studies. Regardless, inclusion of this non-US data in labeling would not be appropriate, as it is unlikely to be informative to the US population of users. The data to be reported in labeling is shown in Table 2.

³⁶ Upadhyay UD, Desai S, LIDAR V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. *Obstet Gynecol* 2015; 125(1): 175-183

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Table 2 Common Adverse Events (≥ 15%) in US Studies of the Proposed Dosing Regimen

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

Source: Data from Middleton³, Winikoff⁴ and Winikoff⁹

Team Leader Comment:

The Applicant noted that bleeding and cramping are part of the expected effect of the treatment regimen, and therefore were not typically ascertained or reported as adverse reactions. I agree that it is appropriate to exclude these effects from labeling in Section 6.1.

8.3 SUBMISSION-SPECIFIC SAFETY ISSUES

8.3.1 Uterine Rupture

As discussed in the primary review, the potential risk of uterine rupture was considered because the current labeling for misoprostol includes a Boxed Warning against the use of misoprostol for gestations > 8 weeks due to the risk of uterine rupture. Although misoprostol is used alone for various obstetric indications, including induction of labor at term, it was important to consider whether labeling about this potential risk is warranted for Mifeprex. Both (b) (6) and the (b) (6) ((b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports. The literature review identified two studies in first trimester gestation that evaluated the risk of uterine rupture in over 500 women who received 800 mcg of misoprostol to evacuate the uterus. Although 144 women in the studies had a previous uterine scar (a known risk factor for uterine rupture), no ruptures occurred in either study. Three case reports of uterine rupture with mifepristone/misoprostol treatment in the first trimester were identified (see Table 3).

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Table 3 Case Reports of Uterine Rupture with Mifepristone/Misoprostol in the First Trimester

Study	GA (weeks)	Mifepristone used?	Dose of Misoprostol	Number of doses of misoprostol	Risk Factor for Rupture
Khan ³⁷	8	Yes; dose not specified	600 mcg	1	1 prior C-section, 1 prior uterine rupture at 32 weeks
Bika ³⁸	10 2/7	Yes; 200 mg	800 mcg x 2 doses then 400 mcg x 2 doses	4	2 prior C-sections
Willmott ³⁹	12 3/7	Yes; 200 mg	400 mcg	5	none

Source: modified from (b) (6) table in the primary review

The FAERS search did not identify any reports of uterine rupture with use of mifepristone alone. Of 80 reports, 77 cited use of misoprostol alone, and three of mifepristone and misoprostol. Only two reports of uterine rupture in the first trimester were identified, both using misoprostol alone; one entailed an unspecified dose and route of misoprostol at 5 weeks gestation, and one involved vaginal administration of 800 mcg misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar.

Team Leader Comment:

The risk of uterine rupture with first trimester use of mifepristone and misoprostol appears to be extremely rare, and most often associated with a prior uterine scar, a known risk factor for uterine rupture. Labeling of these reports is warranted, but no restriction of use is needed based upon this extremely rare adverse reaction.

8.4 LABORATORY TESTING & VITAL SIGNS

The studies evaluated did not describe laboratory testing or evaluation of vital signs. Lab tests that are commonly performed for medical abortion include confirmation of pregnancy (urine or serum pregnancy testing) as well as Rhesus factor testing, such that RhD immunoglobulin can be administered as indicated.

8.5 POSTMARKETING SAFETY FINDINGS

There is a substantial amount of postmarketing safety data available on Mifeprex due to the reporting requirements under the REMS. The Year 3 REMS Assessment report was submitted by the Applicant in June, 2015.

³⁷ Khan S et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. *Journal of Obstet Gynaecol* 2007; 27: 869-870

³⁸ Bika O, Huned D, Jha S, Selby K Uterine rupture following termination of pregnancy in a scarred uterus *J Obstet Gynaecol* 2014; 34(2): 198-9. doi: 10.3109/01443615.2013.841132

³⁹ Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. *BJOG* 2008;15:575-77

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In addition, the (b) (6) (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. There have been 18 reported deaths in the US, with eight of these associated with sepsis (seven tested positive for *Clostridium sordellii*, one tested positive for *Clostridium perfringens*). Seven of the eight cases involved vaginal use of misoprostol, a practice that is no longer common. There have been an additional 11 foreign deaths reported in this time period, including three in which *Clostridium* was identified. There have been no Clostridial septic deaths reported in the US since 2009, and none worldwide since 2010.

(b) (6) also updated case reports of serious adverse events over the same time period, although this entailed search of two FDA adverse events databases (the previous system, AERS, and the current FAERS), which precludes providing cumulative numbers over the full time period. Details are provided in the primary review. In summary, these data demonstrate that the rates of hospitalizations, severe infections, blood loss requiring transfusion and ectopic pregnancy remain stable and acceptably low.

During its ongoing surveillance of adverse events, (b) (6) did identify a safety signal of anaphylaxis and angioedema, with one case of anaphylaxis reported a few hours after mifepristone administration, and six cases of angioedema, five of which occurred in the context of pregnancy termination, within 24 hours of mifepristone administration (the sixth was in a Cushing's syndrome patient). There were no additional cases reported in the literature.

Team Leader Comment:

I agree with (b) (6) recommendation that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling and for continued pharmacovigilance for these adverse events.

8.6 SPECIAL ISSUES RELATIVE TO THIS NDA

8.6.1 REMS Modifications

As discussed previously, the current REMS consists of the following elements:

- Medication Guide
- Elements to Assure Safe Use (ETASU)
 - ETASU A: Special certification of healthcare providers who prescribe Mifeprex, completion of a Prescriber's Agreement and enrollment in the REMS program
 - ETASU C: Mifeprex dispensed only in certain healthcare settings (clinics, medical offices or hospitals) by or under the supervision of a specially certified prescriber; not distributed to or dispensed through retail pharmacies
 - ETASU D: Patients must complete and sign a Patient Agreement; a copy to be placed in the patient chart and a copy of the Agreement and the Medication Guide to 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.

After review of the modifications proposed by the Sponsor, the modifications that would be needed to harmonize with planned labeling changes, and after broad discussion of the need

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for various elements of the current REMS, (b) (6) recommended and the Division agreed to the following, for reasons that are discussed in Section 6.1:

- Removal of the phrase “under Federal law” from the Prescriber’s Agreement (Prescriber’s Agreement Form) (see further discussion of this change in Section 7.7.2)
- Replacement of references to “physician” with “healthcare provider who prescribes” (see further discussion of this change in Section 7.5)
- Removal of the Medication Guide from the REMS – (b) (6) agrees that distribution of the Medication Guide as part of patient labeling will ensure that patients receive this educational tool, and that requiring provision of the Medication Guide under the REMS is not necessary
- Revision of the Prescriber’s Agreement (now called the Prescriber’s Agreement Form) – the requirement for certification remains, and the criteria that a provider must meet to become a certified prescriber have not changed. The provider reporting requirement has been changed to mandate reporting only of deaths (currently reporting of ongoing pregnancies, hospitalizations, transfusions or other serious adverse events is required). Reference to the Patient Agreement should be removed.
- Removal of the Patient Agreement form – (b) (6) concurs with the recommendation for removal of the Patient Agreement from the REMS, for the reasons outlined in the (b) (6) review. In addition, the Prescriber’s Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have. FDA has removed REMS requirements in other programs based on the integration of the REMS safe use condition into clinical practice.
- Revision of the REMS goals to state that the goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by a) requiring healthcare providers who prescribe to be certified in the Mifeprex REMS program, and b) ensuring that Mifeprex is only dispensed in certain healthcare settings under the supervision of a certified prescriber

8.6.2 Advocacy Group Communications

The Agency received three letters from representatives from academia and various professional organizations, including the American Congress of Obstetricians and Gynecologists, the American Public Health Association (APHA), the National Abortion Federation (NAF), Ibis Reproductive Health and Gynuity. In general, these advocates requested FDA to revise labeling in a manner that would reflect current clinical practice, including the new dose regimen submitted by the Sponsor, and proposing to extend the gestational age through 70 days. Other requests were that the labeling not require that the drug-taking location for both Mifeprex and misoprostol be restricted to the clinic, and that labeling not specify that an in-person follow-up visit is required. The advocates also requested that any licensed healthcare provider should be able to prescribe Mifeprex 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. The letters cited articles that were also submitted by the Applicant and are reviewed above.

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8.7 OVERALL ASSESSMENT OF PROPOSED CHANGES

My overall evaluation of the Applicant's proposed changes is provided here, categorized as changes for which we could rely upon evidenced-based support, and as regulatory decisions that are not based on review of data.

Evidence-based Changes:

1. Change to Mifeprex and misoprostol doses, change in the dosing regimen, including misoprostol route of administration from oral to buccal and change in dosing interval between Mifeprex and misoprostol and the place in which the woman may take misoprostol

Numerous studies evaluated the proposed doses of Mifeprex and misoprostol and the buccal route of administration for misoprostol, including in gestations through 70 days. The studies support that this revised regimen is safe and effective. (b) (4)

. It is important to note, however, that removal of the current regimen from labeling does not reflect any concerns about the safety or efficacy of that regimen.

There is a substantial body of literature assessing the dosing interval between Mifeprex and misoprostol; while it appears that intervals < 24 hours may be associated with a higher failure rate, the revised window of 24-48 hours after Mifeprex in which misoprostol may be taken maintains an acceptable level of safety and efficacy of the regimen.

A large number of the studies reviewed allowed for home administration of misoprostol, and a systematic review of studies including over 45,000 women, half of which incorporated home use of misoprostol, found very similar rates of treatment success and of ongoing pregnancy regardless of whether misoprostol was taken in-clinic or at home. Therefore, there is no clinical reason to restrict the location in which misoprostol may be taken. Given the fact that the onset of cramping and bleeding occurs rapidly (i.e., generally within 2 hours) after misoprostol dosing, allowing dosing at home increases the chance that the woman will be in an appropriate location when the process begins.

2. Inclusion of an option to administer a second dose of misoprostol to women who do not have a complete expulsion of the pregnancy at follow-up

Many studies included in the treatment regimen the option for a second dose of misoprostol for women who had not completed the expulsion of the products of conception by follow-up, and some specifically evaluated the success of a second dose. The available data support the safety and efficacy of a repeat dose of misoprostol if complete expulsion of the products of conception has not occurred but the pregnancy is not ongoing. The ability to offer this option may reduce the need for surgical intervention. While there is a suggestion that the success rate following a second dose of misoprostol may be somewhat lower at more advanced gestational ages, there is no evidence that the practice of offering an additional dose results in adverse effects.

Surgical evacuation of the uterus is still recommended in labeling in the case of an ongoing pregnancy.

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3. Change in the gestational age through which the Mifeprex regimen has been found to be safe and effective for use

Of the studies that supported the proposed changes in the dosing regimen, four of them, including almost 3,000 women, evaluated the safety and effectiveness of the regimen in women through 70 days gestation. A number of additional studies supported safety and effectiveness of the regimen for gestations later than the currently labeled 49 days but < 64 days.

4. Change in timing and description of follow-up

A large systematic review supported the appropriateness of follow-up assessment being made as soon as 7 days through 14 days after Mifeprex administration.

A number of studies evaluated different follow-up modalities and demonstrated that there are a variety of acceptable alternatives to in-clinic follow-up that can identify cases in which there is need for additional intervention. The labeling will not be directive regarding specific details of how follow-up will be performed; that will be a decision made between the healthcare provider and patient.

5. Change in who may be a certified provider

The Applicant noted that the training and qualification of who can perform medical abortion is regulated on the state level, with 15 states having laws that specifically permit non-physician providers (such as nurse practitioners, physician assistants and certified nurse-midwives) to provide medical abortion. Studies that evaluated the proposed dosing regimen given by non-physicians demonstrated continued high rates of success at gestational ages through 70 days, as compared to care provided by physicians. The data on use by non-physician healthcare providers, therefore, support that it is safe and effective to permit healthcare providers who are licensed to prescribe medications to prescribe and administer Mifeprex, provided they meet the requirements for certification described in the REMS.

6. Change in labeling describing the time to expulsion of products of conception

Data were reviewed that support the revised description of the time interval during which expulsion of the products of conception typically occurs as 2-24 hours. Providing accurate information in labeling will aid the woman in ensuring she is in an appropriate setting when expulsion is likely to occur.

Regulatory Changes:

1. Addition of misoprostol to the indication statement in the Indication and Use section of labeling

Inclusion of misoprostol in the indication statement is appropriate because all the data reviewed for this supplement and for the original Mifeprex application was based on a treatment regimen that included both drugs. Current FDA labeling practice is to include information in the indication statement if the labeled drug is to be used only in conjunction with another therapy.

2. Removal of the term “under Federal law” from two sections of the Prescriber’s Agreement

The Division and (b) (6) were unable determine a rationale for the inclusion of this phrase. The phrase appears redundant, because all of the requirements under the REMS are imposed

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as a matter of Federal law. There is no precedent for this terminology in other REMS documents; therefore, it should be removed.

9. Advisory Committee Meeting

The original application for Mifeprex was the subject of a meeting of the Reproductive Health Drugs Advisory Committee in July 1996, which resulted in a vote of 6-0 (with 2 abstentions) that the benefits outweighed the risk for this product. An Advisory Committee meeting was not requested for this efficacy supplement because there were no complex scientific or other issues on which input from outside experts was needed.

10. Pediatrics

This application triggered PREA because it addresses a new dosing regimen. The Applicant requested a waiver of pediatric studies in females < 12 years of age because the indication is not relevant to this premenarcheal population. The Applicant stated that safety and efficacy data are available for over 300 adolescent patients aged 12 to 16 years. As discussed in the primary review, Gatter¹² included data on 322 adolescents from 11 through 16 years old (106 of whom were under 16 years) and on 283 17 year olds, which demonstrated efficacy similar to (even numerically greater than) that of the entire study population. No pediatric cases required transfusion, hospitalization or treatment for severe infection. Upadhyay³⁶ looked at abortion-related complications by age, with the lowest category being ≤ 19 years and found no statistical difference and a nominally lower rate for the younger females compared to women aged 20-24 years; however, this included both medical and surgical abortions.

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

The Applicant did not have specific data on adherence in any age group, but stated that the equivalent levels of efficacy for females < 17 years compared to females ≥ 17 years indicates that there is no clinically significant difference in adherence by age. As for follow-up, the Applicant provided information from four studies (Gatter¹², Cameron^{40, 41}, Ngoc⁴², Horning⁴³), which included a total of 346 females < 17 years, with most of the data coming from Gatter. For the females < 17 years, adherence to follow-up ranged from 78-100%, and averaged 78.6%, while for females ≥ 17 years, adherence ranged from 77-96%, and averaged

⁴⁰ Cameron ST, Glasier A, Dewarta H, Johnstone A, Burnside A. Telephone follow-up and self-performed urine pregnancy testing after early medical abortion: a service evaluation. *Contraception* 2012; 86: 67-73

⁴¹ Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? *Contraception* 2015; 91: 6-11

⁴² Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. *Obstet Gynecol* 2014; 123: 88-95

⁴³ Horning EL, Chen BA, Meyn LA, Creinin MD. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. *Contraception* 2012; 85: 402-407

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13.3 RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES

I concur with the changes to the REMS program described in Section 8.6.1, which include:

- Provision for “healthcare providers who prescribe” who meet the qualifications specified in the REMS to become certified and thereby allowed to order, prescribe and administer Mifeprex
- Revision of the Prescriber’s Agreement (now called the Prescriber’s Agreement Form) to reflect labeling revisions pursuant to this efficacy supplement
- Removal of the Patient Agreement from the REMS
- Removal of the Medication Guide from the REMS
- Revision of the provider reporting requirements to require reporting only of deaths to the Applicant
- Removal of the term “under Federal law” from the Prescriber’s Agreement

13.4 RECOMMENDATION FOR OTHER POSTMARKETING STUDY REQUIREMENTS AND COMMITMENTS

I concur with [REDACTED]^{(b) (6)} that no postmarketing study requirements or commitments are warranted.

13.5 RECOMMENDED COMMENTS TO APPLICANT

None

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Appendix 1

Table 4 Summary Table of Studies Supporting NDA 20-687, Supplement 020

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
Revision of Dosing Regimen (doses, ROA, dosing interval)								
Winikoff 2012 US	OL prospective trial	729 (56-63 days: 379 64-70 days: 350)	57-70 days	2 nd dose of miso allowed for incomplete Ab		Regimen, <i>Home miso</i> , GA	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: 0.6% Hospitalization: 0.6% Sepsis 0.2% Common AEs reported
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1 st dose		Regimen, GA	Total: 97.7% ≤ 49: 97.8% 50-63: 93.7% 64-70: 96.2% Total ongoing preg: 0.7%	Hospitalization
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		Regimen, <i>Other HCPs</i>	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD group hosp for bleed underwent SA No transfusion Hospitalization
Sanhueza Smith 2015 Mexico	Observational	1,001 (≤ 56 days: 622 57-63 days: 196 64-70 days: 183)	70 days			Regimen, GA	≤ 56: 94.9% 57-63: 90.0% 64-70: 91.2% Success in ≤ 56 arm signif > in 57-63 arm	Serious AEs not described

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
		151)						
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		Regimen	Total: 96.6%	Infection 0.01-0.6% Transfusions 0.6% Hospitalization 0.9% Buccal vs. oral ↓nausea, ↑diarrhea, fever, dizziness
						GA	≤49: 98.1% 50-56: 96.7% 57-63: 95.2% 64-70: 93.1%	
						Dose interval	Overall: 24 hr: 94.2% 24-48 hr: 96.8% ≤49 days: 24 hr: 96.8% 24-48 hr: 98.2% 50-63 days: 24 hr: 92.1% 24-48 hr: 96.3% All comparisons sig different	
						2 nd dose miso	91-100% success	
Chong 2015 US	Prospective, non-randomized, OL study	400 (128 took Mife at home; 272 in clinic)	63 days			Regimen	Clinic use: 96.9% Home use: 96.3% NS different	Hospitalization AEs NR
Gatter 2015 US	Observational	13,373	63 days			Regimen, GA, Adolescents	Total: 97.7% 22-28: 97.3% 29-35: 98.8%	Odds of needing aspiration ↑ at higher GA

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
							36-42: 98.8% 43-49: 98.1% 50-56: 96.9% 57-63: 95.5% Total ongoing preg: 0.5%	Infx req'g hospitalization 0.01% Total hospital 0.04% Transfusion 0
Grossman, Grindley et al. 2011 US	Prospective cohort	578 (281 telemedicine, 297 face-to-face)	63 days			Home miso	Face-to-face group: 96.9% Telemed group: 98.7%	No deaths or hospitalization transfusion 0.
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2 nd dose of miso allowed for incomplete Ab		Regimen, MAB vs. SAB (additional dose, home miso)	MAB 99.6% SAB 99.8%	Hospitalization visit, uterine perforation, infection, transfusion – in total, NS dif
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	Regimen, home miso	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported; Fever/chills m frequent with
					GA	Buccal: ≤ 42: 98.7% 43-49: 96.4% 50-56: 95.7% 57-63: 94.8%		
Alam 2013 Bangladesh	Prospective study of menstrual regulation	651	63 days			Regimen	93% (in 606 women with documented)	Common ARs reported

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
							pregnancy at tx)	
Blum, Raghavan et al. 2012 Tunisia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			Regimen, <i>home miso</i>	Total: 92.9%	Serious AEs not discussed
						GA	≤ 49: 96.3% 50-56: 86.5% 57-63: 96.3%	
Chai 2013 Hong Kong	DB RCT	90 (45 in each arm)	63 days			Regimen: Buccal vs. SL miso	Buccal: 95.4% SL: 97.8% NS different Both ROAs had 100% success in GA ≤ 49 days	AEs similar except chills sig higher in SL arm
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen	Total: 96.4% (Either dose)	↑ AEs in 800 arm Vomiting 22% Fever/chills 33%
						GA	≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%	
						2 nd dose of miso	92% success	
Giri 2011 Nepal	Prospective	100	63 days			Regimen	Total 93.6%	No transfusion or hospitalization
Goldstone 2012 Australia	Retro observational	13,345	63 days			Regimen, <i>home miso</i>	96.5% Ongoing preg: 0.6%	1 death from stroke (<0.01%) Infection w/o transfusion 0.2% Hemorrhage 0.2% Transfusion 0.2%
Louie 2014 Azerbaijan	Observational	863	63 days			Regimen, Home miso	92% selected home misoprostol; overall success	Common AEs reported

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
							97%	
						GA	Total: 97% ≤ 49: 97% 50-56: 99% 57-63: 96%	
Ngo 2012 Vietnam	Retrospective	337 (167 on proposed regimen)	63 days	Additional 200 mcg miso dose given if no bleeding by 3 hours post-miso; dose repeated again if no bleeding 2 hours later		Regimen: proposed vs. "Chinese regimen" of 150 mg Mife over 2 days, 600 mcg miso on Day 3	Proposed: 91.0% Chinese: 77.7% Add'l miso dose needed (1 dose): Proposed: 7.8% Chinese: 21.8% Add'l miso dose needed (2 doses): Proposed: 0% Chinese: 2.9%	AEs NR
Ngoc 2014 Vietnam	RCT	1,433 (713 to phone f/u; 720 to clinic f/u)	63 days			Regimen, <i>follow-up</i>	Phone arm: 94.8% Clinic arm: 94.6%	
Ngoc 2011 Vietnam	RCT	400 (Mife + miso: 202, miso-alone: 198)	63 days			Proposed regimen vs. miso-alone (home miso for both)	Proposed regimen: 96.5%	
		Proposed regimen by GA:				GA	Proposed regimen:	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
		≤ 49: 162 50-56: 28 57-63: 11					≤ 49: 97.5% 50-56: 89.3% 57-63: 100%	
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)	63 days	2 nd dose of miso offered for incomplete Ab		Regimen, home miso	97.3%	Common AEs reported
		GA				≤49: 98.0% 50-56: 96.8% 57-63: 95.9%		
Creinin 2007 US	RCT	1,128	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: miso WITH Mife or 24 hrs later	Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2 nd miso dose)	Higher rates of nausea, diarrhea, warmth/chills immediate miso SAEs: transfusion 0.4% (all in 24 hr group); acute infx, treated 0.9% (equally each group)
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145				GA	24-hr interval; only a single miso dose: ≤ 49: 94.3% 50-56: 93.0% 57-63: 94.5% (NS trend)	
Creinin 2004 US	RCT	1,080	63 days	Add'l dose of miso if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: 6-8 hrs vs. 23-25 hrs after Mife	6-8 hrs vs. 1 day: NS diff 6-8 hr: 95.8% 1 day: 98.1% (incl Ss who got a 2 nd miso dose)	Side effects of the interval b/w 6-8 hr and miso were higher in the 24 hr group; rates of nausea & vom after miso doses were also sig. in the 23-25 hr
		N in 24-hr interval arm by GA:				GA	24-hr interval (1 or more miso doses):	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
		≤ 49: 258 50-56: 157 57-63: 116					≤ 49: 98.4% 50-56: 97.5% 57-63: 98.3%	group. Transfusion 0 (equal across Hosp for PID 0 (only in 6-8 hr group)
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273)	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	Regimen (ROA)	Buccal: 97.1%	No hospitaliza Common AEs reported
		GA				Buccal: ≤ 49: 96.6% 50-63: 100%		
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		Regimen	Total: 95.2%; 1.1% ongoing preg Miso ≥ 800 mcg buccal: 96.8%; 0.7% ongoing preg	Hospitalizatio 0.3% Transfusion: 0
Wedisinghe 2010 US (4) UK (1)	Literature review (5 RCTs)	5,139	49-63 days	1 of 5 studies (N=49) used 600 mife + 400 oral miso	Vaginal miso	Dose interval	Pooled analysis: risk of failure for 0-24 hr vs. 24-72 hrs: 1.054 NS Trend for lower success if < 8 hour interval	NR

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
Fjerstad, Sivin et al 2009 US	Retrospective	1,638 (1,349 for proposed regimen; 334 oral miso)	59 days			Proposed regimen vs. oral miso in subset \leq 49 days (both miso doses taken at home) <i>Proposed regimen by GA</i>	Proposed regimen: 98.3% Oral miso: 96.8% 28-34 days: 99.3% 35-41: 98.8% 42-48: 98.1% 49-55: 98.3% 56-59: 95.7%	
Middleton 2005 US	OL RCT	442 (buccal 223, vaginal 219)	56 days			Regimen (buccal vs. vaginal miso)	Buccal: 95% Vaginal: 93% NS different Ongoing preg: Buccal: 0.9% Vaginal: 1.9%)	Transfusion 0 (buccal); Endometritis (all vaginal miso) Similar rates of common AEs diarrhea sig. more common with
Dahiya 2012 India	RCT	100 (miso + mife: 50, miso alone 50)	56 days			Proposed regimen vs. miso alone	Proposed regimen: 92%; no missed Ab or continued preg	
Kulier 2011 Global	Cochrane systematic review of RCTs (58 studies; 4 comparing mife dose)			200 vs. 600 mg mife;	Oral, vaginal, SL, buccal miso	Dose regimen	Mife 200 mg as effective as 600 mg; oral miso less effective than vaginal; SL & buccal miso as effective as vaginal but \uparrow	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
							AEs	
Home Dosing of Misoprostol								
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2 nd dose of miso allowed for incomplete Ab		Regimen, Home miso, GA	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: 0.6% Hospitalization: 0.6% Sepsis 0.2% Common AEs reported
Abbas 2015 – Global	Literature review (6 studies, 4 using 800 mcg buccal miso)	For 800 mcg buccal miso: 781 at 57-63 days, 480 at 64-70 days)	70 days	400 mcg (& 800 mcg)	Vaginal & SL (& buccal) miso	GA, Home miso	Total over 4 studies of 800 buccal: 57-63: 93.5% 64-70: 92.5%	
Grossman, Grindley et al. 2011 US	Prospective cohort	578 (281 telemedicine, 297 face-to-face)	63 days			Home miso	Face-to-face group: 96.9% Telemed group: 98.7%	No deaths or hospitalization transfusion 0.6%
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2 nd dose of miso allowed for incomplete Ab		Regimen, MAB vs. SAB (additional dose, home miso)	MAB 99.6% SAB 99.8%	Hospitalization 0.6%, visit, uterine perforation, infection, transfusion – in total, NS diff
Winikoff 2008 US	OL RCT	966 (847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	Regimen, home miso	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported; Fever/chills more frequent with oral

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
						GA	<i>Buccal:</i> ≤ 42: 98.7% 43-49: 96.4% 50-56: 95.7% 57-63: 94.8%	
Blum, Raghavan et al. 2012 Tunisia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			Regimen, home miso	Total: 92.9%	Serious AEs not discussed
						GA	≤ 49: 96.3% 50-56: 86.5% 57-63: 96.3%	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen (included option for home miso)	Total: 96.4% (Either dose)	↑ AEs in 800 arm Vomiting 22% Fever/chills 33%
						GA	800 mcg dose: ≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%	
						2 nd dose of miso	2 nd dose (all GA, both miso dose arms): 92% success N unspecified	
Goldstone 2012 Australia	Retro observational	13,345	63 days			Regimen, home miso	96.5%	Transfusion 0 1 death from s (<0.01%) Infection w/o s

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
								Hemorrhage C
Louie 2014 Azerbaijan	Observational	863	63 days			Home miso	92% selected home misoprostol; overall success 97%	Common AEs reported
						GA	Total: 97% ≤ 49: 97% 50-56: 99% 57-63: 96%	
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)	63 days	2 nd dose of miso offered for incomplete Ab		Regimen, home miso	Total: 97.3% 94.9% with single miso dose	Common AEs reported
						GA	≤49: 98.0% 50-56: 96.8% 57-63: 95.9%	
Creinin 2007 US	RCT	1,128 (immediate miso: 567; 24 hours later at home: 561)	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: miso WITH Mife or 24 hrs later at home; home use	Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2 nd miso dose)	Higher rates of nausea, diarrhea, warmth/chills immediate miso SAEs: transfusion 0.4% (all in 24 group); acute infx, treated 0.9% (equally each group)
						GA	24-hr interval; only a single miso dose:	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
		≤ 49: 229 50-56: 172 57-63: 145					≤ 49: 94.3% 50-56: 93.0% 57-63: 94.5% (NS trend)	
Swica 2013 US	Observational	301 (139 chose home mife; 162 chose clinic mife)	63 days	6-48 hour dose interval	RoA for miso not specified	Home miso	Clinic use of mife: 95.6% Home use of mife: 96.7% NS different	1 hospitalization other SAEs Common AEs
Kopp Kallner 2010 Sweden	Prospective observational	395 (203 < 50 d; 192 50-63 d)	63 days		Vaginal miso	Home miso, GA	< 50: 98% 50-63: 96.9%	No SAEs, transfusions of serious infx
Lokeland 2014 Norway	Prospective observational	1,018	63 days		Vaginal miso	Home miso, GA	Success + no unplanned visits: 93.6% (no data by GA)	Surgery: < 49: 4.1% 49-55: 3.2% 56-63: 8.1% Transfusion 0 Aspiration for bleeding 8%
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		Regimen		Hospitalization 0.3% Transfusion: 0
						Home miso (in-clinic administration required or not)	Failure rate: In-clinic - Yes: 5.2% No: 4.5% Ongoing pregnancy: In-clinic - Yes: 1.0% No: 1.2% No evidence of	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
							higher failure rate in logistic regression model if in-clinic admin was not required	
Additional Dose of Misoprostol								
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2 nd dose of miso allowed for incomplete Ab		Regimen, Home miso, GA	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: 0.6% Hospitalization 0.6% Sepsis 0.2% Common AEs reported
						2 nd dose of miso	57-63: 91% (N=11) 64-70: 66.7% (N=9)	
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1 st dose		Regimen, 2 nd dose of miso	2 nd dose: 80% success (N=5)	
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		2 nd dose miso	2 nd dose: 91-100% success	Infection 0.01% Transfusions 0.6% Hospitalization 0.9% Buccal vs. oral ↓nausea, ↑diarrhea fever, dizziness
Bracken 2014	Prospective comparative	703 (389 at 57-63)	70 days	400 mcg miso	SL miso	GA	57-63: 94.8% 64-70: 91.9%	2 nd dose of miso bleeding or

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
Ukraine, Rep. of Georgia, India, Tunisia	OL	days, 325 at 64-70 days)				2 nd dose of miso	2nd dose: 57-63: 90.9% (N=22) 64-70: 86.3% (N=34)	incomplete M... 57-63: 5.7% 64-70: 10.5% Surgery for excessive/pro... bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for bleee... 57-63: 0.5% 64-70: 0.3% Transfusion: 57-63: 0.3% 64-70: 0.3%
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	2 nd dose of miso part of regimen	2 nd dose: Buccal: 92.9% (N=14)	Common AEs reported; Fever/chills m... frequent with
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen	Total: 96.4% (Either dose)	↑ AEs in 800 a... Vomiting 22% Fever/chills 33%
						GA	800 mcg dose: ≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%	
						2 nd dose of miso	2 nd dose (all GA, both miso dose arms):	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
							92% success N unspecified	
Louie 2014 Azerbaijan	Observational	863	63 days			Home miso	92% selected home misoprostol; overall success 97%	Common AEs reported
Reeves 2008 US	Pooled secondary analysis of 2 RCTs	1,972	63 days		Vaginal miso	2 nd dose miso	2 nd dose: 62% success N=68	
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273) Buccal by GA: ≤ 49: 226 50-63: 38	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	Regimen (ROA)	Buccal: 97.1%	No hospitalizations Common AEs reported
						GA	Buccal: ≤ 49: 96.6% 50-63: 100%	
						2 nd dose of miso	100% (N=2, both in buccal arm)	
Coyaji 2007 India	RCT, placebo control	300 (150 in each arm)	56 days	400 mcg miso vs. 2 doses 400 mcg w/in 3 hours	Oral miso	2 nd dose of miso	1 dose: 86% 2 doses: 92% Contin'd preg: 1 dose: 7% 2 doses: 1%	Surg for bleed no difference
Increased Gestational Age								

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2 nd dose of miso allowed for incomplete Ab		Regimen, Home miso, GA	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: 0.6% Hospitalization: 0.6% Sepsis 0.2% Common AEs reported
Boersma 2011 Curacao	Prospective observational	330 (< 49: 199, 50-63: 105, 64-70: 26)	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1 st dose		Regimen, GA	Total: 97.7% ≤ 49: 97.8% 50-63: 95.8% 64-70: 96.2%	
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		Regimen, Other HCPs	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD group hosp for bleed underwent SA No transfusion Hospitalization
Sanhueza Smith 2015 Mexico	Observational	1,001 (622 ≤ 56 days, 196 57-63 days, 151 64-70 days)	70 days			Regimen, GA	≤ 56: 94.9% 57-63: 90.0% 64-70: 91.2% Success in ≤ 56 arm signif > in 57-63 arm	Serious AEs not described
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		GA	Total: 96.6% ≤49: 98.1% 50-56: 96.7% 57-63: 95.2% 64-70: 93.1%	Infection 0.01% Transfusions 0.6% Hospitalization 0.9% Buccal vs. oral ↓nausea, ↑diarrhea
						Dose interval	24 hr: 94.2% 24-48 hr: 96.8%	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
						2 nd dose miso	91-100% success	fever, dizziness
Gouk 1999 UK	Prospective observational	253 (127 at 64-70 days)	63-83 days		Vaginal miso	GA	Overall: 94.5% 64-70: 94.5%	Common AEs reported
Bracken 2014 Ukraine, Rep. of Georgia, India, Tunisia	Prospective comparative OL	703 (389 at 57-63 days, 325 at 64-70 days)	70 days	400 mcg miso	SL miso	GA	57-63: 94.8% 64-70: 91.9%	2 nd dose of miso bleeding or incomplete M. 57-63: 5.7% 64-70: 10.5% Surgery for excessive/prolonged bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for bleed: 57-63: 0.5% 64-70: 0.3% Transfusion: 57-63: 0.3% 64-70: 0.3%
Abbas 2015 – Global	Literature review (6 studies, 4 using 800 mcg buccal miso)	For 800 mcg buccal miso: 781 at 57-63 days, 480 at 46-70 days)	70 days	400 mcg (& 800 mcg)	Vaginal & SL (& buccal) miso	GA, home miso	Total over 4 studies of 800 buccal: 57-63: 93.5% 64-70: 92.5%	
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal,	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	Regimen, home miso	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal	Common AEs reported; Fever/chills more frequent with

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
		426 oral)					<i>arm</i>	
Blum, Raghavan et al. 2012 Tunisia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			<i>Regimen, home miso</i>	<i>Total: 92.9%</i>	Serious AEs not discussed
						GA	≤ 49: 96.3% 50-56: 86.5% 57-63: 96.3%	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		<i>Regimen</i>	<i>Total: 96.4% (Either dose)</i>	↑ AEs in 800 arm Vomiting 22% Fever/chills 33%
						GA	≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%	
						<i>2nd dose of miso</i>	<i>92% success</i>	
Louie 2014 Azerbaijan	Observational	863	63 days			<i>Home miso (92%)</i>	92% selected home misoprostol; overall success 97%	Common AEs reported
						GA	≤ 49: 97% 50-56: 99% 57-63: 96%	
Ngoc 2011 Vietnam	RCT	400 (Mife + miso: 202, miso-alone: 198)	63 days			<i>Proposed regimen vs. miso-alone (home miso for both)</i>	<i>Proposed regimen: 96.5%</i>	
		Proposed regimen by GA: ≤ 49: 162 50-56: 28 57-63: 11				GA Proposed regimen: ≤ 49: 97.5% 50-56: 89.3% 57-63: 100%		

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)	63 days	2 nd dose of miso offered for incomplete Ab		Regimen, home miso	97.3%	Common AEs reported
						GA	≤49: 98.0% 50-56: 96.8% 57-63: 95.9%	
Creinin 2007 US	RCT	1,128 With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: miso WITH Mife or 24 hrs later	Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2 nd miso dose)	Higher rates of nausea, diarrhea, warmth/chills immediate miso SAEs: transfusion 0.4% (all in 24 hr group); acute infection, treated 0.9% (equally each group)
						GA	24-hr interval; only a single miso dose: ≤ 49: 94.3% 50-56: 93.0% 57-63: 94.5% (NS trend)	
Creinin 2004 US	RCT	1,080 N in 24-hr interval arm by GA: ≤ 49: 258 50-56: 157 57-63: 116	63 days	Add'l dose of miso if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: 6-8 hrs vs. 23-25 hrs after Mife	6-8 hrs vs. 1 day: NS diff 6-8 hr: 95.8% 1 day: 98.1% (incl Ss who got a 2 nd miso dose)	Side effects of the interval b/w and miso were higher in the 24 hr group; rate of nausea & vom after miso doses were also sig. in the 23-25 hr group. Transfusion 0 (equal across
						GA	24-hr interval (1 or more miso doses): ≤ 49: 98.4% 50-56: 97.5% 57-63: 98.3%	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
								Hosp for PID (only in 6-8 hr group)
Kopp Kallner 2010 Sweden	Prospective observational	395 (203 < 50 d; 192 50-63 d)	63 days		Vaginal miso	Home miso, GA	< 50: 98% 50-63: 96.9%	No SAEs, transfusions or serious infx
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273)	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	Regimen (ROA)	Buccal: 97.1%	No hospitalizations Common AEs reported
		GA				Buccal: ≤ 49: 96.6% 50-63: 100%		
Fjerstad, Sivin et al 2009 US	Retrospective	1,638 (1,349 for proposed regimen; 334 oral miso)	59 days			Proposed regimen vs. oral miso in subset ≤ 49 days (both miso doses taken at home)	Proposed regimen: 98.3% Oral miso: 96.8%	
						Proposed regimen by GA	28-34 day: 99.3% 35-41: 98.8% 42-48: 98.1% 49-55: 98.3% 56-59: 95.7%	
Method of Follow-up								
Ngoc 2014 Vietnam	RCT	1,433 (713 to phone f/u; 720 to clinic f/u)	63 days			Regimen	Phone arm: 94.8% Clinic arm: 94.6%	Phone f/u: Sens: 92.8% Spec: 90.6% UPT alone:
						Follow-up: phone + semi-quant UPT 2 weeks after Mife vs. in-clinic f/u		

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
								Sens: 95.7%
Perriera 2010 US	Prospective cohort	139	63 days		Buccal (N=6) or vaginal (N=127) miso	Follow-up: phone f/u @ 7 days + HSUP @ 30 days		Successful f/u 97.1% Prediction per phone f/u: Sens: 95.9% Spec: 50% PPV: 97.5% NPV: 37.5% Transfusion 1 Hospitalization infx 0.7%
Blum, Shochet et al. 2012 US	Open-label trial	490	63 days	Not specified	Not specified	Follow-up: at-home semi-quant UPT vs. in-clinic	20% LTFU; 97.5% success;	Sens: 100% Spec: 97% PPV: 9.1% NPV: 100% Screen+: 3.1%
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		Regimen	Total: 95.2%; 1.1% ongoing preg Miso ≥ 800 mcg buccal: 96.8%; 0.7% ongoing preg	Hospitalization 0.3% Transfusion: 0
						Time of f/u	Logistic regression – no difference in	

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
							failure rate by time of f/u (< 1 week vs. ≥ 1 wk)	
Rossi 2004 US	Secondary analysis of RCT	1,080	63 days		Vaginal miso; 6-8 hr vs. 23-25 hr interval	Follow-up (pt assess vs. HCP assess vs. sono)		Pt: Sens 96.5% Spec 31.3% NPV 98.8% PPV 13.5%
Cameron 2015 Scotland	Retro database review	1,726	63 days		Vaginal miso	Follow-up (LSUP + sx + guidance on when to call clinic)	Ongoing preg: 0.5%	Unsched/eme visit: 2% (mainly bleeding)
Cameron 2012 Scotland	Practice evaluation	616 (476 for phone, 140 for sono)	63 days		Vaginal miso	Follow-up (phone + LSUP vs. sono)		Phone: 87% contacted; 85% screen - screen + Sens 75% Spec 86% NPV 99.7% PPV 6%
Michie 2014 Scotland	Retrospective database review	943	63 days		Vaginal miso	Follow-up: phone call + home LSUP		Sens: 100% Spec: 88% PPV: 3.6% NPV: 100%
Oppegaard 2014 Austria, Scandinavia	RCT, non-inferiority	924 (466 clinic f/u; 458 self-assess)	63 days		Vaginal miso	Follow-up (clinic vs. at-home semi-quant hCG)		Pregs undetected hCG: 0.7%; LTFU NS difference
Lynd 2013 Vietnam	Observational	300	63 days	Unspecified	Unspecified	Follow-up (Home semi-quant UPT)		Sens: 100% Spec: 89.7% PPV: 27.5% NPV: 100%

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
								Screen+: 13.3
Fiala 2003 Austria	Observational	217	49 days	600 mg mife, 400 mcg miso; Add'l dose of miso if no bleeding w/in 3 hrs of 1 st dose	Oral miso	Follow-up (sono vs. hCG)	Total: 98.2%	2 aspirations hemorrhage
						2 nd dose of miso	N=28 Success rate not provided	
Healthcare Provider								
Puri 2015 Nepal	Non-equivalent comparison	596 (307 in NM arm, 289 in "standard care" arm)	Not specified, but notes MAB is legal to 84 days			Other HCPs	Incomplete abortions: NM: 1.6% "Standard care": 2.4%	No SAEs
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		Regimen, 2 nd dose miso, Other HCPs	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD g hosp for bleed underwent SA No transfusion Hospitalization
Kopp Kallner 2015 Sweden	RCT - equivalence	1,180 (481 CNM, 457 MD)	63 days			Other HCPs	CNM: 99% MD: 97.4%	No serious complications transfusions
Warriner 2011 Nepal	RCT - equivalence	1,104 (542 nurse/NM; 535 MD)	63 days		Vaginal miso	Other HCPs	Ongoing preg or incomplete MAB: Nurse: 2.6% MD: 3.7%	No hospitaliza or bleeding re transfusion
Adolescents								
Gatter 2015 US	Observational	13,373	63 days			Regimen, GA	Total: 97.7% 22-28: 97.3% 29-35: 98.8%	Odds of needi aspiration ↑ at higher GA

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Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings
		By age: < 18: 605 18-24: 6,684 25-29: 3,317 30-34: 1,613 35-39: 855 40+: 299				Data on 322 females age 11-16 years and 283 age 17 years	36-42: 98.8% 43-49: 98.1% 50-56: 96.9% 57-63: 95.5% Success by age: < 18: 98.7% 18-24: 98.1% 25-29: 97.5% 30-34: 96.5% 35-39: 97.0% 40+: 97.3%	Infx req'g hospitalization 0.01% Total hospital 0.04% Transfusion 0
Phelps 2001 US	Prospective	28 (Age 14-17)	56 days		Vaginal miso	Adolescents	100%	Common AEs effects") reported "no AEs"
Niinimaki 2011 Finland	Population-based retro cohort	27,030 (3,024 adolescents)	20 weeks (85% ≤ 84 days)	Unspecified (Mife + a prostaglandin analog)	Unspecified	Adolescent AEs	Incomplete Ab 6.9% Surgical evacuation 10.7%	AE rates ↓ in adolescents ORs for: Hemorrhage 0 Incomplete Ab Surgical evac No deaths
Other Topics								
Upadhyay 2015 US	Retro cohort	11,319 (MAB)	63 days	Not specified	Not specified	AEs		Any abortion-complication: Major complication 0.31%

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(C)NM = (certified) nurse-midwife; HSUP= high-sensitivity urine pregnancy test; LSUP= low-sensitivity urine pregnancy test; LTFU = lost to follow-up; MAB = medical abortion; NR = not reported; NS = non-significant; OL = open-label; PID = pelvic inflammatory disease; RCT = randomized controlled trial; RoA = route of administration; UPT = urine pregnancy test

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Table of Studies for 20-687

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Revision of Dosing Regimen (doses, ROA, dosing interval)									
Winikoff 2012 US	OL prospective trial	729 (56-63 days: 379 64-70 days: 350)	57-70 days	2 nd dose of miso allowed for incomplete Ab		Regimen, <i>Home miso</i> , GA	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: 0.5% Hospitalization: 0.6% Sepsis 0.2% Common AEs reported	13-14% LTFU Data includes women w/repeat miso
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1 st dose		Regimen, GA	Total: 97.7% ≤ 49: 97.8% 50-63: 93.7% 64-70: 96.2% Total ongoing preg: 0.7%	Hospitalization 0.7%	
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		Regimen, <i>Other HCPs</i>	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD group: hosp for bleeding, underwent SAB No transfusions Hospitalization 0.1%	
Sanhueza Smith 2015 Mexico	Observational	1,001 (≤ 56 days: 622 57-63 days: 196 64-70 days: 151)	70 days			Regimen, GA	≤ 56: 94.9% 57-63: 90.0% 64-70: 91.2% Success in ≤ 56 arm signif > in 57-63 arm	Serious AEs not described	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		Regimen	Total: 96.6%	Infection 0.01-0.5% Transfusions 0.03-0.6% Hospitalization 0.04-0.9% Buccal vs. oral: ↓nausea, ↑diarrhea, fever, dizziness	Majority of data from proposed regimen
						GA	≤49: 98.1% 50-56: 96.7% 57-63: 95.2% 64-70: 93.1%		
						Dose interval	Overall: 24 hr: 94.2% 24-48 hr: 96.8% ≤49 days: 24 hr: 96.8% 24-48 hr: 98.2% 50-63 days: 24 hr: 92.1% 24-48 hr: 96.3% All comparisons sig different		
						2 nd dose miso	91-100% success		
Chong 2015 US	Prospective, non-randomized, OL study	400 (128 took Mife at home; 272 in clinic)	63 days			Regimen	Clinic use: 96.9% Home use: 96.3% NS different	Hospitalization 0.6% AEs NR	Objective was studying home use of Mife
Gatter 2015 US	Observational	13,373	63 days			Regimen, GA, Adolescents	Total: 97.7% 22-28: 97.3% 29-35: 98.8% 36-42: 98.8% 43-49: 98.1% 50-56: 96.9%	Odds of needing aspiration ↑ at higher GA Infx req'g hospitalization 0.01%	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
							57-63: 95.5% Total ongoing preg: 0.5%	Total hospitalization 0.04% Transfusion 0.03%	
Grossman, Grindley et al. 2011 US	Prospective cohort	578 (281 telemedicine, 297 face-to-face)	63 days			Home miso	Face-to-face group: 96.9% Telemed group: 98.7%	No deaths or hospitalizations, transfusion 0.2%	21-24% LTFU
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2 nd dose of miso allowed for incomplete Ab		Regimen, MAB vs. SAB (additional dose, home miso)	MAB 99.6% SAB 99.8%	Hospitalization, ED visit, uterine perforation, infection, transfusion – 0.1% in total, NS different	Not included in efficacy labeling
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	Regimen, home miso	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported; Fever/chills more frequent with buccal	9.5% LTFU
						GA	Buccal: ≤ 42: 98.7% 43-49: 96.4% 50-56: 95.7% 57-63: 94.8%		
Alam 2013 Bangladesh	Prospective study of menstrual regulation	651	63 days			Regimen	93% (in 606 women with documented pregnancy at tx)	Common ARs reported	
Blum, Raghavan et	DB RCT, placebo	441 (220)	63 days			Regimen, home miso	Total: 92.9%	Serious AEs not discussed	
						GA	≤ 49: 96.3%		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
al. 2012 Tunisia & Vietnam	control	mife/miso, 221 miso only)					50-56: 86.5% 57-63: 96.3%		
Chai 2013 Hong Kong	DB RCT	90 (45 in each arm)	63 days			Regimen: Buccal vs. SL miso	Buccal: 95.4% SL: 97.8% NS different Both ROAs had 100% success in GA ≤ 49 days	AEs similar except chills sig higher in SL arm	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36- 48 hours		Regimen	Total: 96.4% (Either dose)	↑ AEs in 800 arm: Vomiting 22% Fever/chills 33%	
						GA	≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%		
						2 nd dose of miso	92% success		
Giri 2011 Nepal	Prospective	100	63 days			Regimen	Total 93.6%	No transfusions or hospitalizations	
Goldstone 2012 Australia	Retro observational	13,345	63 days			Regimen, home miso	96.5% Ongoing preg: 0.6%	1 death from sepsis (<0.01%) Infection w/o sepsis 0.2% Hemorrhage 0.1% Transfusion 0.1%	
Louie 2014 Azerbaijan	Observational	863	63 days			Regimen, Home miso	92% selected home misoprostol; overall success 97%	Common AEs reported	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
						GA	Total: 97% ≤ 49: 97% 50-56: 99% 57-63: 96%		
Ngo 2012 Vietnam	Retrospective	337 (167 on proposed regimen)	63 days	Additional 200 mcg miso dose given if no bleeding by 3 hours post-miso; dose repeated again if no bleeding 2 hours later		Regimen: proposed vs. "Chinese regimen" of 150 mg Mife over 2 days, 600 mcg miso on Day 3	Proposed: 91.0% Chinese: 77.7% Add'l miso dose needed (1 dose): Proposed: 7.8% Chinese: 21.8% Add'l miso dose needed (2 doses): Proposed: 0% Chinese: 2.9%	AEs NR	
Ngoc 2014 Vietnam	RCT	1,433 (713 to phone f/u; 720 to clinic f/u)	63 days			Regimen, <i>follow-up</i>	Phone arm: 94.8% Clinic arm: 94.6%		Ngoc 2014 Vietnam
Ngoc 2011 Vietnam	RCT	400 (Mife + miso: 202, miso-alone: 198) Proposed regimen by GA: ≤ 49: 162 50-56: 28 57-63: 11	63 days			Proposed regimen vs. miso-alone (home miso for both) GA	Proposed regimen: 96.5% Proposed regimen: ≤ 49: 97.5% 50-56: 89.3% 57-63: 100%		
Pena 2014	OL	1,000	63 days	2 nd dose of		Regimen, home miso	97.3%	Common AEs	94.9% with

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Mexico	prospective cohort	(by GA: ≤49: 551 50-56: 247 57-63: 171)		miso offered for incomplete Ab				reported	single miso dose
						GA	≤49: 98.0% 50-56: 96.8% 57-63: 95.9%		
Creinin 2007 US	RCT	1,128	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: miso WITH Mife or 24 hrs later	Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2 nd miso dose)	Higher rates of nausea, diarrhea, warmth/chills with immediate miso. SAEs: transfusion 0.4% (all in 24-hour group); acute pelvic infx, treated as outpt 0.9% (equally in each group)	Looking at only a single miso dose, success for immediate vs. 1 day was 91% vs. 94%; did not meet n-i criteria.
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145					GA		
Creinin 2004 US	RCT	1,080	63 days	Add'l dose of miso if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: 6-8 hrs vs. 23-25 hrs after Mife	6-8 hrs vs. 1 day: NS diff 6-8 hr: 95.8% 1 day: 98.1% (incl Ss who got a 2 nd miso dose)	Side effects during the interval b/w Mife and miso were sig. higher in the 23-25 hr group; rates of nausea & vomiting after miso dose were also sig. higher in the 23-25 hr group. Transfusion 0.2% (equal across arms); Hosp for PID 0.2% (only in 6-8 hr	Looking at only a single miso dose, success for 6-8 hr vs. 1 day was 94.9% vs. 97.2%
		N in 24-hr interval arm by GA: ≤ 49: 258 50-56: 157 57-63: 116					GA		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
								group)	
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273)	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	Regimen (ROA)	Buccal: 97.1%	No hospitalizations Common AEs reported	
		GA				Buccal: ≤ 49: 96.6% 50-63: 100%			
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		Regimen	Total: 95.2%; 1.1% ongoing preg Miso ≥ 800 mcg buccal: 96.8%; 0.7% ongoing preg	Hospitalization: 0.3% Transfusion: 0.1%	Risk factors for failure: GA > 56 days, interval < 23 hours, oral vs. other RoA, 400 mcg vs. higher doses
Wedisinghe 2010 US (4) UK (1)	Literature review (5 RCTs)	5,139	49-63 days	1 of 5 studies (N=49) used 600 mife + 400 oral miso	Vaginal miso	Dose interval	Pooled analysis: risk of failure for 0-24 hr vs. 24-72 hrs: 1.054 NS Trend for lower success if < 8 hour interval	NR	4 with proposed doses include Creinin 2004 & 2007, Guest 2007 & Schaff 2000
Fjerstad, Sivin et al 2009	Retrospective	1,638 (1,349 for proposed)	59 days			Proposed regimen vs. oral miso in subset ≤ 49 days (both miso	Proposed regimen: 98.3% Oral miso: 96.8%		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
US		regimen; 334 oral miso)				doses taken at home) <i>Proposed regimen by GA</i>	28-34 days: 99.3% 35-41: 98.8% 42-48: 98.1% 49-55: 98.3% 56-59: 95.7%		
Middleton 2005 US	OL RCT	442 (buccal 223, vaginal 219)	56 days			Regimen (buccal vs. vaginal miso)	Buccal: 95% Vaginal: 93% NS different Ongoing preg: Buccal: 0.9% Vaginal: 1.9%)	Transfusion 0.5% (buccal); Endometritis 0.9% (all vaginal miso) Similar rates of common AEs except diarrhea sig. more common with buccal	
Dahiya 2012 India	RCT	100 (miso + mife: 50, miso alone 50)	56 days			Proposed regimen vs. miso alone	Proposed regimen: 92%; no missed Ab or continued preg		
Kulier 2011 Global	Cochrane systematic review of RCTs (58 studies; 4 comparing mife dose)			200 vs. 600 mg mife;	Oral, vaginal, SL, buccal miso	Dose regimen	Mife 200 mg as effective as 600 mg; oral miso less effective than vaginal; SL & buccal miso as effective as vaginal but ↑ AEs		
Home Dosing of Misoprostol									
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at	57-70 days	2 nd dose of miso allowed for incomplete Ab		Regimen, Home miso, GA	57-63: 93.5% 64-70: 92.8% Ongoing preg	Transfusion: 0.5% Hospitalization: 0.6%	13-14% LTFU Data includes

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
		64-70 days)					3% at each GA	Sepsis 0.2% Common AEs reported	women w/ repeat miso
Abbas 2015 – Global	Literature review (6 studies, 4 using 800 mcg buccal miso)	For 800 mcg buccal miso: 781 at 57-63 days, 480 at 64-70 days)	70 days	400 mcg (& 800 mcg)	Vaginal & SL (& buccal) miso	GA, Home miso	Total over 4 studies of 800 buccal: 57-63: 93.5% 64-70: 92.5%		Sanhueza Winkoff 2012 Boersma Pena
Grossman, Grindley et al. 2011 US	Prospective cohort	578 (281 telemedicine, 297 face-to-face)	63 days			Home miso	Face-to-face group: 96.9% Telemed group: 98.7%	No deaths or hospitalizations, transfusion 0.2%	21-24% LTFU
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2 nd dose of miso allowed for incomplete Ab		Regimen, MAB vs. SAB (additional dose, home miso)	MAB 99.6% SAB 99.8%	Hospitalization, ED visit, uterine perforation, infection, transfusion – 0.1% in total, NS different	
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	Regimen, home miso	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported; Fever/chills more frequent with buccal	
						GA	Buccal: ≤ 42: 98.7% 43-49: 96.4% 50-56: 95.7% 57-63: 94.8%		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Blum, Raghavan et al. 2012 Tunisia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			Regimen, home miso	Total: 92.9%	Serious AEs not discussed	
						GA	≤ 49: 96.3% 50-56: 86.5% 57-63: 96.3%		
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen (included option for home miso)	Total: 96.4% (Either dose)	↑ AEs in 800 arm: Vomiting 22% Fever/chills 33%	# of women opting for home miso not specified
						GA	800 mcg dose: ≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%		
						2 nd dose of miso	2 nd dose (all GA, both miso dose arms): 92% success N unspecified		
Goldstone 2012 Australia	Retro observational	13,345	63 days			Regimen, home miso	96.5%	Transfusion 0.1% 1 death from sepsis (<0.01%) Infection w/o sepsis Hemorrhage 0.1%	
Louie 2014 Azerbaijan	Observational	863	63 days			Home miso	92% selected home misoprostol; overall success 97%	Common AEs reported	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
						GA	Total: 97% ≤ 49: 97% 50-56: 99% 57-63: 96%		
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)	63 days	2 nd dose of miso offered for incomplete Ab		Regimen, home miso	Total: 97.3% 94.9% with single miso dose	Common AEs reported	
						GA	≤49: 98.0% 50-56: 96.8% 57-63: 95.9%		
Creinin 2007 US	RCT	1,128 (immediate miso: 567; 24 hours later at home: 561)	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: miso WITH Mife or 24 hrs later at home; home use	Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2 nd miso dose)	Higher rates of nausea, diarrhea, warmth/chills with immediate miso. SAEs: transfusion 0.4% (all in 24-hour group); acute pelvic infx, treated as outpt 0.9% (equally in each group)	Looking at only a single miso dose, success for immediate vs. 1 day was 91% vs. 94%; did not meet n-i criteria.
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145				GA	24-hr interval; only a single miso dose: ≤ 49: 94.3% 50-56: 93.0% 57-63: 94.5% (NS trend)		
Swica 2013 US	Observational	301 (139 chose home mife; 162 chose	63 days	6-48 hour dose interval	RoA for miso not specified	Home miso	Clinic use of mife: 95.6% Home use of mife: 96.7%	1 hospitalization, no other SAEs Common AEs NR	Objective was studying home use

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
		clinic mife)					NS different		of <u>Mife</u>
Kopp Kallner 2010 Sweden	Prospective observational	395 (203 < 50 d; 192 50-63 d)	63 days		Vaginal miso	Home miso, GA	< 50: 98% 50-63: 96.9%	No SAEs, transfusions or serious infx	
Lokeland 2014 Norway	Prospective observational	1,018	63 days		Vaginal miso	Home miso, GA	Success + no unplanned visits: 93.6% (no data by GA)	Surgery: < 49: 4.1% 49-55: 3.2% 56-63: 8.1% Transfusion 0.1%; Aspiration for bleeding 8%	
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		<i>Regimen</i>		Hospitalization: 0.3% Transfusion: 0.1%	Risk factors for failure: GA > 56 days, interval < 23 hours, oral vs. other RoA, 400 mcg vs. higher doses
						Home miso (in-clinic administration required or not)	Failure rate: In-clinic - Yes: 5.2% No: 4.5% Ongoing pregnancy: In-clinic - Yes: 1.0% No: 1.2% No evidence of higher failure rate in logistic regression model if in-clinic admin was not required		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Additional Dose of Misoprostol									
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2 nd dose of miso allowed for incomplete Ab		Regimen, Home miso, GA	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: 0.5% Hospitalization: 0.6% Sepsis 0.2% Common AEs reported	13-14% LTFU Data includes women w/ repeat miso
						2 nd dose of miso	57-63: 91% (N=11) 64-70: 66.7% (N=9)		
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1 st dose		Regimen, 2 nd dose of miso	2 nd dose: 80% success (N=5)		
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		2 nd dose miso	2 nd dose: 91-100% success	Infection 0.01-0.5% Transfusions 0.03-0.6% Hospitalization 0.04-0.9% Buccal vs. oral: ↓nausea, ↑diarrhea, fever, dizziness	Majority of data from proposed regimen
Bracken 2014	Prospective comparative	703 (389 at 57-63)	70 days	400 mcg miso	SL miso	GA	57-63: 94.8% 64-70: 91.9%	2 nd dose of miso for bleeding or	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Ukraine, Rep. of Georgia, India, Tunisia	OL	days, 325 at 64-70 days)				2 nd dose of miso	2 nd dose: 57-63: 90.9% (N=22) 64-70: 86.3% (N=34)	incomplete MAB: 57-63: 5.7% 64-70: 10.5% Surgery for excessive/prolonged bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for bleeding: 57-63: 0.5% 64-70: 0.3% Transfusion: 57-63: 0.3% 64-70: 0.3%	
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	2 nd dose of miso part of regimen	2 nd dose: Buccal: 92.9% (N=14)	Common AEs reported; Fever/chills more frequent with buccal	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen	Total: 96.4% (Either dose)	↑ AEs in 800 arm: Vomiting 22% Fever/chills 33%	
						GA	800 mcg dose: ≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%		
						2 nd dose of miso	2 nd dose (all GA, both miso dose arms): 92% success		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
							N unspecified		
Louie 2014 Azerbaijan	Observational	863	63 days			Home miso	92% selected home misoprostol; overall success 97%	Common AEs reported	
Reeves 2008 US	Pooled secondary analysis of 2 RCTs	1,972	63 days		Vaginal miso	2 nd dose miso	2 nd dose: 62% success N=68		Creinin 2004 Creinin 2007 Did not evaluate 2 nd dose in orig papers
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273) Buccal by GA: ≤ 49: 226 50-63: 38	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	Regimen (ROA)	Buccal: 97.1%	No hospitalizations Common AEs reported	
						GA	Buccal: ≤ 49: 96.6% 50-63: 100%		
						2 nd dose of miso	100% (N=2, both in buccal arm)		
Coyaji 2007 India	RCT, placebo control	300 (150 in each arm)	56 days	400 mcg miso vs. 2 doses 400 mcg w/in 3 hours	Oral miso	2 nd dose of miso	1 dose: 86% 2 doses: 92% Contin'd preg: 1 dose: 7% 2 doses: 1%	Surg for bleeding – no difference	Limited relevance due to different regimen
Increased Gestational Age									
Winikoff 2012	OL prospective	729 (379 at 56-63)	57-70 days	2 nd dose of miso allowed		Regimen, Home miso, GA	57-63: 93.5% 64-70: 92.8%	Transfusion: 0.5% Hospitalization:	13-14% LTFU

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
US	trial	days, 350 at 64-70 days)		for incomplete Ab			Ongoing preg 3% at each GA	0.6% Sepsis 0.2% Common AEs reported	Data includes women w/repeat miso
Boersma 2011 Curacao	Prospective observational	330 (< 49: 199, 50-63: 105, 64-70: 26)	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1 st dose		Regimen, GA	Total: 97.7% ≤ 49: 97.8% 50-63: 95.8% 64-70: 96.2%		
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		Regimen, Other HCPs	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD group: hosp for bleeding, underwent SAB No transfusions Hospitalization 0.1%	
Sanhueza Smith 2015 Mexico	Observational	1,001 (622 ≤ 56 days, 196 57-63 days, 151 64-70 days)	70 days			Regimen, GA	≤ 56: 94.9% 57-63: 90.0% 64-70: 91.2% Success in ≤ 56 arm signif > in 57-63 arm	Serious AEs not described	
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		GA	Total: 96.6% ≤49: 98.1% 50-56: 96.7% 57-63: 95.2% 64-70: 93.1%	Infection 0.01-0.5% Transfusions 0.03-0.6% Hospitalization 0.04-0.9% Buccal vs. oral: ↓nausea, ↑diarrhea, fever, dizziness	Majority of data from proposed regimen
						Dose interval	24 hr: 94.2% 24-48 hr: 96.8%		
						2 nd dose miso	91-100% success		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Gouk 1999 UK	Prospective observational	253 (127 at 64-70 days)	63-83 days		Vaginal miso	GA	Overall: 94.5% 64-70: 94.5%	Common AEs reported	
Bracken 2014 Ukraine, Rep. of Georgia, India, Tunisia	Prospective comparative OL	703 (389 at 57-63 days, 325 at 64-70 days)	70 days	400 mcg miso	SL miso	GA	57-63: 94.8% 64-70: 91.9%	2 nd dose of miso for bleeding or incomplete MAB: 57-63: 5.7% 64-70: 10.5% Surgery for excessive/prolonged bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for bleeding: 57-63: 0.5% 64-70: 0.3% Transfusion: 57-63: 0.3% 64-70: 0.3%	
Abbas 2015 – Global	Literature review (6 studies, 4 using 800 mcg buccal miso)	For 800 mcg buccal miso: 781 at 57-63 days, 480 at 46-70 days)	70 days	400 mcg (& 800 mcg)	Vaginal & SL (& buccal) miso	GA, home miso	Total over 4 studies of 800 buccal: 57-63: 93.5% 64-70: 92.5%		Sanhueza Winkoff 2012 Boersma Pena
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	Regimen, home miso	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported; Fever/chills more frequent with buccal	9.5% LTFU
Blum,	DB RCT,	441	63 days			Regimen, home miso	Total: 92.9%	Serious AEs not	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Raghavan et al. 2012 Tunisia & Vietnam	placebo control	(220 mife/miso, 221 miso only)				GA	≤ 49: 96.3% 50-56: 86.5% 57-63: 96.3%	discussed	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen	Total: 96.4% (Either dose)	↑ AEs in 800 arm: Vomiting 22% Fever/chills 33%	
						GA	≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%		
						2 nd dose of miso	92% success		
Louie 2014 Azerbaijan	Observational	863	63 days			Home miso (92%)	92% selected home misoprostol; overall success 97%	Common AEs reported	
						GA	≤ 49: 97% 50-56: 99% 57-63: 96%		
Ngoc 2011 Vietnam	RCT	400 (Mife + miso: 202, miso-alone: 198)	63 days			Proposed regimen vs. miso-alone (home miso for both)	Proposed regimen: 96.5%		
		Proposed regimen by GA: ≤ 49: 162 50-56: 28 57-63: 11				GA Proposed regimen: ≤ 49: 97.5% 50-56: 89.3% 57-63: 100%			
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551)	63 days	2 nd dose of miso offered for incomplete		Regimen, home miso	97.3%	Common AEs reported	94.9% with single miso dose
						GA	≤49: 98.0%		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
		50-56: 247 57-63: 171)		Ab			50-56: 96.8% 57-63: 95.9%		
Creinin 2007 US	RCT	1,128	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	<i>Dose interval: miso WITH Mife or 24 hrs later</i>	<i>Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2nd miso dose)</i>	Higher rates of nausea, diarrhea, warmth/chills with immediate miso. SAEs: transfusion 0.4% (all in 24-hour group); acute pelvic infx, treated as outpt 0.9% (equally in each group)	Looking at only a single miso dose, success for immediate vs. 1 day was 91% vs. 94%; did not meet n-i criteria.
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145				GA	24-hr interval; only a single miso dose: ≤ 49: 94.3% 50-56: 93.0% 57-63: 94.5% (NS trend)		
Creinin 2004 US	RCT	1,080	63 days	Add'l dose of miso if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	<i>Dose interval: 6-8 hrs vs. 23-25 hrs after Mife</i>	<i>6-8 hrs vs. 1 day: NS diff 6-8 hr: 95.8% 1 day: 98.1% (incl Ss who got a 2nd miso dose)</i>	Side effects during the interval b/w Mife and miso were sig. higher in the 23-25 hr group; rates of nausea & vomiting after miso dose were also sig. higher in the 23-25 hr group. Transfusion 0.2% (equal across arms); Hosp for PID 0.2% (only in 6-8 hr group)	Looking at only a single miso dose, success for 6-8 hr vs. 1 day was 94.9% vs. 97.2%
		N in 24-hr interval arm by GA: ≤ 49: 258 50-56: 157 57-63: 116				GA	24-hr interval (1 or more miso doses): ≤ 49: 98.4% 50-56: 97.5% 57-63: 98.3%		
Kopp	Prospective	395	63 days		Vaginal	Home miso, GA	< 50: 98%	No SAEs,	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Kallner 2010 Sweden	observational	(203 < 50 d; 192 50-63 d)			miso		50-63: 96.9%	transfusions or serious infx	
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273)	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	Regimen (ROA)	Buccal: 97.1%	No hospitalizations Common AEs reported	
		GA				Buccal: ≤ 49: 96.6% 50-63: 100%			
Fjerstad, Sivin et al 2009 US	Retrospective	1,638 (1,349 for proposed regimen; 334 oral miso)	59 days			Proposed regimen vs. oral miso in subset ≤ 49 days (both miso doses taken at home)	Proposed regimen: 98.3% Oral miso: 96.8%		
						Proposed regimen by GA	28-34 day: 99.3% 35-41: 98.8% 42-48: 98.1% 49-55: 98.3% 56-59: 95.7%		
Method of Follow-up									
Ngoc 2014 Vietnam	RCT	1,433 (713 to phone f/u; 720 to clinic f/u)	63 days			Regimen	Phone arm: 94.8% Clinic arm: 94.6%		
						Follow-up: phone + semi-quant UPT 2 weeks after Mife vs. in-clinic f/u	Phone f/u: Sens: 92.8% Spec: 90.6% UPT alone: Sens: 95.7%		
Perriera 2010 US	Prospective cohort	139	63 days		Buccal (N=6) or vaginal (N=127)	Follow-up: phone f/u @ 7 days + HSUP @ 30 days		Successful f/u: 97.1% Prediction per	ROA difference irrelevant b/c

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
					miso			phone f/u: Sens: 95.9% Spec: 50% PPV: 97.5% NPV: 37.5% Transfusion 1.4% Hospitalization for infx 0.7%	studying f/u
Blum, Shochet et al. 2012 US	Open-label trial	490	63 days	Not specified	Not specified	Follow-up: at-home semi-quant UPT vs. in-clinic	20% LTFU; 97.5% success;	Sens: 100% Spec: 97% PPV: 9.1% NPV: 100% Screen+: 3.1%	Blum, Shochet et al. 2012 US
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		Regimen	Total: 95.2%; 1.1% ongoing preg Miso ≥ 800 mcg buccal: 96.8%; 0.7% ongoing preg	Hospitalization: 0.3% Transfusion: 0.1%	Risk factors for failure: GA > 56 days, interval < 23 hours, oral vs. other RoA, 400 mcg vs. higher doses
						Time of f/u	Logistic regression – no difference in failure rate by time of f/u (< 1 week vs. ≥ 1 wk)		
Rossi 2004 US	Secondary analysis of RCT	1,080	63 days		Vaginal miso; 6-8 hr vs. 23-25 hr interval	Follow-up (pt assess vs. HCP assess vs. sono)		Pt: Sens 96.5% Spec 31.3% NPV 98.8%	Different ROA ok since f/u

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
								PPV 13.5%	
Cameron 2015 Scotland	Retro database review	1,726	63 days		Vaginal miso	Follow-up (LSUP + sx + guidance on when to call clinic)	Ongoing preg: 0.5%	Unsched/emerg visit: 2% (mainly for bleeding)	
Cameron 2012 Scotland	Practice evaluation	616 (476 for phone, 140 for sono)	63 days		Vaginal miso	Follow-up (phone + LSUP vs. sono)		Phone: 87% contacted; 85% screen - 15% screen + Sens 75% Spec 86% NPV 99.7% PPV 6%	
Michie 2014 Scotland	Retrospective database review	943	63 days		Vaginal miso	Follow-up: phone call + home LSUP		Sens: 100% Spec: 88% PPV: 3.6% NPV: 100%	
Oppegaard 2014 Austria, Scandinavia	RCT, non-inferiority	924 (466 clinic f/u; 458 self-assess)	63 days		Vaginal miso	Follow-up (clinic vs. at-home semi-quant hCG)		Pregs undetected by hCG: 0.7%; LTFU NS different	Different ROA ok since f/u
Lynd 2013 Vietnam	Observational	300	63 days	Unspecified	Unspecified	Follow-up (Home semi-quant UPT)		Sens: 100% Spec: 89.7% PPV: 27.5% NPV: 100% Screen+: 13.3%	Unspec regimen ok since relates to f/u
Fiala 2003 Austria	Observational	217	49 days	600 mg mife, 400 mcg miso; Add'l dose of miso if no bleeding w/in 3 hrs of 1 st dose	Oral miso	Follow-up (sono vs. hCG) 2 nd dose of miso	Total: 98.2% N=28 Success rate not provided	2 aspirations for hemorrhage	
Healthcare Provider									

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Puri 2015 Nepal	Non-equivalent comparison	596 (307 in NM arm, 289 in “standard care” arm)	Not specified, but notes MAB is legal to 84 days			Other HCPs	Incomplete abortions: NM: 1.6% “Standard care”: 2.4%	No SAEs	
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		Regimen, 2 nd dose miso, Other HCPs	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD group: hosp for bleeding, underwent SAB No transfusions Hospitalization 0.1%	
Kopp Kallner 2015 Sweden	RCT - equivalence	1,180 (481 CNM, 457 MD)	63 days			Other HCPs	CNM: 99% MD: 97.4%	No serious complications or transfusions	
Warriner 2011 Nepal	RCT - equivalence	1,104 (542 nurse/NM; 535 MD)	63 days		Vaginal miso	Other HCPs	Ongoing preg or incomplete MAB: Nurse: 2.6% MD: 3.7%	No hospitalizations or bleeding req'g transfusion	
Adolescents									
Gatter 2015 US	Observational	13,373	63 days			Regimen, GA	Total: 97.7% 22-28: 97.3% 29-35: 98.8% 36-42: 98.8% 43-49: 98.1% 50-56: 96.9% 57-63: 95.5%	Odds of needing aspiration ↑ at higher GA Infx req'g hospitalization 0.01% Total hospitalization 0.04% Transfusion 0.03%	Applicant obtained GA-stratified
		By age: < 18: 605 18-24: 6,684 25-29: 3,317							

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
		30-34: 1,613 35-39: 855 40+: 299					30-34: 96.5% 35-39: 97.0% 40+: 97.3%		data from authors
Phelps 2001 US	Prospective	28 (Age 14-17)	56 days		Vaginal miso	Adolescents	100%	Common AEs (“side effects”) reported “no AEs”	
Niinimaki 2011 Finland	Population-based retro cohort	27,030 (3,024 adolescents)	20 weeks (85% ≤ 84 days)	Unspecified (Mife + a prostaglandin analog)	Unspecified	Adolescent AEs	Incomplete Ab 6.9% Surgical evacuation 10.7%	AE rates ↓ in adolescents ORs for: Hemorrhage 0.87 Incomplete Ab 0.69 Surgical evac 0.78 No deaths	
Other Topics									
Upadhyay 2015 US	Retro cohort	11,319 (MAB)	63 days	Not specified	Not specified	AEs		Any abortion-related complication: 5.19% Major complication 0.31%	Limited value since regimen not specified

(C)NM = (certified) nurse-midwife; HSUP= high-sensitivity urine pregnancy test; LSUP= low-sensitivity urine pregnancy test; LTFU = lost to follow-up; MAB = medical abortion; NR = not reported; NS = non-significant; OL = open-label; PID = pelvic inflammatory disease; RCT = randomized controlled trial; RoA = route of administration; UPT = urine pregnancy test

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(b) (6)

04/06/2016

This table was inadvertently truncated when appended to my original CDTL review and is included here for completeness.

EXHIBIT F

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s020

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 29, 2016
Subject	Summary Review
NDA #/Supplement #	20687/S-020
Applicant name	Danco Laboratories, LLC
Date of submission	May 28, 2015
Date of submission receipt	May 29, 2015
PDUFA goal date	March 29, 2016
Proprietary name/established name	Mifeprex/mifepristone
Dosage form/strength	Oral tablet/200 mg
Dosage regimen	Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol
Proposed indication	Mifeprex is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation
Action	Approval

- 1. Introduction**
- 2. Background**
- 3. CMC**
- 4. Nonclinical Pharmacology/Toxicology**
- 5. Clinical Pharmacology**
- 6. Clinical Microbiology**
- 7. Efficacy/Statistics**
- 8. Safety**
- 9. Advisory Committee Meeting**
- 10. Pediatrics**
- 11. Other Relevant Regulatory Issues**
- 12. Labeling**
- 13. Decision/Action/Risk Benefit Assessment**

1. Introduction

Danco Laboratories, LLC, referred to hereafter as the Applicant, submitted an efficacy supplement (S-020) to NDA 20687 for Mifeprex (mifepristone). The Applicant sought the following changes to its approved application:

1. (b) (4) Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally; see below:
 - Day One: Mifeprex Administration (oral)
One 200 mg tablet of Mifeprex is taken in a single oral dose
 - After a 24-48 hour interval: Misoprostol Administration (buccal)(minimum 24-hour interval between Mifeprex and misoprostol)
Four 200 mcg tablets (total dose: 800 mcg) of misoprostol are taken by the buccal route
2. Removal of the instruction that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex
5. Increase in the maximum gestational age from 49 days to 70 days
6. Change of the labeled time for expected expulsion of pregnancy from 4-24 hours to 2-24 hours post misoprostol administration
7. Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change of “physician” to “healthcare provider” in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change in the indication statement to add reference to use of misoprostol: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation.”
10. Removal of references to “under Federal law” from the Prescriber’s Agreement under the REMS

11. Labeling changes addressing the pediatric requirements under the Pediatric Research Equity Act

This efficacy supplement submission includes information from published studies, review articles and additional information from the authors of some of the publications. These published studies evaluated reproductive age women in the U.S. and outside the U.S. who had early medical termination with mifepristone, in a regimen with misoprostol, including women up through 70 days of gestation.

This memorandum serves as the Division's decisional memorandum for the efficacy supplement.

2. Background

The active ingredient of Mifeprex, mifepristone, is a progestin antagonist. Mifeprex, in a regimen with misoprostol, is approved for the medical termination of pregnancy up through 49 days' gestation. The approved dosing regimen is currently labeled as follows:

- Day 1: The patient takes three 200 mg tablets of Mifeprex in a single oral dose in the clinic, medical office, or hospital.
- Day 3: The patient returns to the clinic, medical office, or hospital and takes two 200 mcg tablets of misoprostol orally.
- Day 14: The patient returns for a follow-up visit to confirm that a complete termination has occurred.

At the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520, requiring that Mifeprex be dispensed only by or under the supervision of a physician who meets certain qualifications. With the passage of FDAAA in 2007, Mifeprex was deemed to have in effect an approved REMS. The Applicant submitted a formal REMS, which was approved on June 8, 2011 and consisted of the following: a Medication Guide, elements to assure safe use (ETASU A [special certification of healthcare providers who prescribe Mifeprex], ETASU C [dispensing only in certain healthcare settings], and ETASU D [safe use condition of a signed Patient Agreement]), an implementation system and a timetable for assessments. The goals of the REMS were 1) To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and 2) 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. The REMS for Mifeprex incorporated the restrictions under which the drug was originally approved.

Since 2011, the Applicant has submitted two REMS assessment reports. The Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

FDA held a pre-NDA meeting with the Applicant on January 29, 2015, to discuss proposed labeling and REMS changes to be submitted in this efficacy supplement. These changes were submitted with the efficacy supplement.

The Applicant submitted published literature and supportive information to support changes to the dose, dosing regimen, gestational age, revisions to labeling, modifications to the REMS document, and to address PREA requirements. The Agency accepts the use of peer reviewed literature as primary data for an application under the framework of a 505(b)(2) application.

3. CMC

No new CMC information was submitted with this efficacy supplement. The CMC team determined no additional review or inspections were required. The CMC team completed a review of the labeling and found the CMC sections of labeling (sections 3, 11 and 16) acceptable (See review dated March 29, 2016). The CMC review team recommends approval of the efficacy supplement; refer also to the CMC review of the separate supplement proposing a single tablet blister pack for Mifeprex, dated January 11, 2016. There are no outstanding CMC issues or postmarketing commitments or requirements.

Comment: On March 10, 2016, a separate CMC supplement was approved that allowed the packaging of individual 200 mg tablets of mifepristone; previously packaging consisted of three 200 mg tablets per blister pack (a total of 600 mg Mifeprex as administered under the originally approved dosing regimen).

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this supplement. The Pharmacology/Toxicology team revised labeling to conform to the Pregnancy and Lactation Labeling Rule. There are no outstanding nonclinical issues. The Pharmacology/Toxicology review team recommends approval of the efficacy supplement; refer to the Pharmacology/Toxicology review dated March 4, 2016.

5. Clinical Pharmacology

The Applicant did not conduct any new clinical pharmacology studies pertaining to the proposed (b) (4) regimen, but provided information on pharmacokinetics (PK) of misoprostol following various routes of administration. The PK of the 200 mg Mifeprex tablet has not been characterized in women, but data are available in men and were submitted in the original NDA. The Clinical Pharmacology review team determined that the PK data were appropriate for inclusion in labeling. Review of the labeling pertinent to the Clinical Pharmacology sections is complete and labeling relevant to pharmacokinetics and pharmacodynamics is acceptable. There are no outstanding Clinical Pharmacology issues or postmarketing commitments or requirements. The clinical pharmacology review team recommends approval of the efficacy supplement; refer to the Clinical Pharmacology review dated March 29, 2016.

6. Clinical Microbiology

Not applicable.

7. Efficacy/Statistics

The Applicant submitted published literature as the primary evidence to support the efficacy (and safety) of the proposed dosing regimen (refer to the Clinical Review dated March 29, 2016, Section 9.5 for a list of submitted references). Most published articles submitted by the Applicant and reviewed by the clinical review team reported the primary efficacy endpoint as complete termination of pregnancy without further medical or surgical intervention; the Division considers this to be a clinically relevant endpoint.

The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent. The clinical review team concluded that the published literature was adequate as the primary information source to support the changes proposed in the efficacy supplement. During the course of the review, the team also requested and received more detailed information from select publications from their authors via communication with the Applicant.

Although there were slight demographic differences among the published studies from the database, these differences were not expected to alter the efficacy or safety of Mifeprex. Therefore, for the majority of the proposed efficacy changes, the clinical team assessed efficacy information from a subset of publications that evaluated a given proposed change. An independent statistical review was not needed for this review of published literature.

The clinical review team identified several major proposed clinical changes in the efficacy supplement. As these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes. These major changes as considered by the clinical team included:

1. A proposed dosing regimen consisting of mifepristone 200 mg orally followed by the buccal administration of 800 mcg misoprostol including:
 - a. Use of a revised interval between mifepristone and misoprostol from 48 hours to 24-48 hours
 - b. Allowing home administration of misoprostol
 - c. Use of an additional dose of misoprostol
2. Support for extending the gestation age through 70 days
3. Flexibility in follow-up visit: follow-up is needed in the range of 7-14 days after Mifeprex administration; the specific nature and exact timing of the follow-up to be agreed upon by the healthcare provider and patient.
4. Change in who can provide Mifeprex from physician to healthcare provider who prescribes

The following section summarizes the clinical review team's evaluations that supported the above proposed changes:

1. *Support for the proposed dose and dosing regimen of 200 mg of Mifeprax orally and 800 mcg of misoprostol buccally 24-48 hours after Mifeprax administration:*
The clinical review team reviewed the submission and identified studies and review articles that evaluated over 35,000 women who were treated with efficacy in the 91-98% range. For additional details on the efficacy from these studies, please refer to Section 6 of the Clinical Review.

2. *Support for extending the gestational age to 70 days:*
The Applicant submitted a number of published articles and systematic reviews that supported the proposed dose and dosing regimen. Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff et al 2012¹, Boersma et al², Sanhueza Smith et al³) and one randomized controlled trial (RCT) (Olavarrieta et al⁴) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin⁵ covered 20 studies including over 30,000 women; all but one of the studies used the proposed regimen in gestations through 70 days (the remaining study used 400 mcg of buccal misoprostol). For those publications that provided overall success rates, these were in the range of 97-98%. Other relevant publications include the systematic review by Raymond⁶ of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of mifepristone. Assessing the efficacy by misoprostol dose, the paper noted that doses \geq 800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%.

¹ Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

² Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011; 16: 61-6

³ Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015; 22: 75-82

⁴ Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousiequez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. *Bull World Health Organ* 2015; 93: 249-258

⁵ Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion *Obstet Gynecol*: a Systematic Review. *Obstet Gynecol* 2015; 126(1): 12-21

⁶ Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

The original dosing regimen specifies taking misoprostol 2 days after Mifeprex. This efficacy supplement proposes a more flexible time frame of 24 to 48 hours between Mifeprex and misoprostol administration. Data from a review article by Wedisinghe et al⁷ evaluated different time intervals using administration of misoprostol after Mifeprex. A meta-analysis of all five studies found a non-significant odds ratio for failure for shorter vs. longer dosing intervals, but a trend for lower success if a dosing interval < 8 hours is used. Chen & Creinin's systematic review⁸ of 20 studies including over 33,000 women, all but one using the proposed regimen, compared the success of dosing intervals of 24 hours with intervals ranging from 24-48 hours. The success rate in six studies that used a 24-hour interval through 63 days gestation was 94.2%, compared to the rate of 96.8% in 14 studies that used a 24-48 hour interval, and this difference was statistically significant. The clinical team concluded that the efficacy of the revised dosing regimen was not compromised by revising the dosing interval to 24-48 hours. In addition, they noted that the overall rate of ongoing pregnancies did not differ significantly by dosing interval.

3. *Administration of misoprostol after Mifeprex administration at home:* Currently, the dosing regimen specifies that misoprostol is taken in the clinic setting following Mifeprex administration. No specific publication evaluated treatment outcomes with use of misoprostol at home compared to in-clinic dosing. However, one large literature review (Raymond et al⁹) evaluated a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration and dosing intervals used in gestations through 63 days. Roughly half of the studies included in this review did not require women to take misoprostol in-clinic. Rates of treatment failure and of ongoing pregnancy were very similar regardless of whether misoprostol was taken in-clinic or at another location. The clinical review team concluded that the review provided sufficient data to support labeling that misoprostol does not need to be restricted to in-clinic administration.
4. *Use of a repeat misoprostol dose, if necessary:* The Applicant submitted several published studies that supported use of a repeat misoprostol dose, when complete uterine expulsion did not occur after the initial misoprostol dose following Mifeprex. In clinical practice, the usual treatment for incomplete expulsion (retained products of conception) may include either a repeat dose of misoprostol, expectant management or a surgical procedure (suction aspiration or a dilation and curettage). Studies that specifically report the success rate of a repeat dose of misoprostol are:

⁷ Wedisinghe L and Elsandabese D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. *Contraception* 2010; 81(4): 269-74. doi: 10.1016/j.contraception.2009.09.007. Epub Oct 29, 2009

⁸ Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004; 103: 851-859

⁹ Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

- Winikoff et al¹⁰ – studied the proposed regimen through 70 days gestation; of the few women who received a second dose for an incomplete abortion at follow-up, the success rate was 91% at 57-63 days and 67% at 64-70 days.
- Chen and Creinin¹¹ – a systematic review of 20 studies, all but one of which used the proposed regimen up through 70 days; success of a second dose ranged from 91-100%
- Boersma et al¹² – included pregnancies through 70 days treated with the proposed regimen; five of 330 women took a second dose due to absence of bleeding 48 hours after first dose; the success rate was 80%
- Louie et al¹³ – studied the proposed regimen to 63 days; in 16 women (of 863) who took a second dose of misoprostol, the success rate was 100%
- Chong et al¹⁴ – compared the proposed regimen to a lower dose of misoprostol; the success of a second dose of misoprostol was 92% overall, but the number of women in each dose arm getting a second dose was not specified.
- Winikoff et al¹⁵ – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%.

Using the information from the above studies and other supportive data, the clinical team concluded that the available data support the efficacy of a repeat dose of misoprostol if complete expulsion has not occurred. The relatively high complete pregnancy termination rates indicate that this option is likely to reduce the need for a surgical intervention.

5. *Requirements regarding follow-up care:* Current labeling states that women will return to the clinic 14 days after Mifeprex administration for follow-up. This provision was based on the follow up regimen in the U.S. phase 3 trial that supported the initial approval in 2000. Although the Applicant submitted several studies that evaluated flexibility in the time of follow-up, the key publication identified by the review team that addressed this issue was a 2013 article by

¹⁰ Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

¹¹ Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004; 103: 851-859

¹² Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011; 16: 61-6

¹³ Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. *Eur J Contracept Reprod Health Care* 2014; 19(6): 457-464

¹⁴ Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. *Contraception* 2012; 86: 251-256

¹⁵ Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008; 112(6): 1303-1310

Raymond¹⁶. The impact of the timing of follow-up was assessed in Raymond's systematic review of studies using various treatment regimens. While some have posited that earlier follow-up may result in a higher rate of surgical intervention (for women who would have had complete expulsion had they been given a bit more time), Raymond's analyses found no difference in failure rates for women followed less than one week after mifepristone as compared to a week or more after mifepristone. As follow-up was anticipated to not alter the efficacy of the proposing dosing regimen, this change is also discussed below in Section 7.

6. *Allowing qualified healthcare providers to use Mifeprex.*

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies included a study by Warriner et al¹⁷ that showed efficacy of 97.4% with nurses versus 96.3% by physicians.

Conclusions: I concur with the clinical review team's assessments and conclusions and these conclusions will be reflected in labeling. The data and information reviewed constitute substantial evidence of efficacy to support the proposed dosing regimen for Mifeprex for pregnancy termination through 70 days gestation. Other proposed changes to the Mifeprex labeling, including the time interval between Mifeprex and misoprostol dosing, and use of a repeat dose, were also adequately supported by evidence. Finally, I concur with the clinical review team that the information from the published literature also supported efficacious use of Mifeprex by non-physician providers.

Comment: Discussion was held as to whether the original dosing regimen approved in 2000 (i.e., Mifeprex 600 mg and misoprostol 400 mcg up to 49 days gestation) should remain in labeling. (b) (4)

(b) (4) the clinical review team and I concur with their (b) (4) request to remove the current regimen from the labeling. Removal of the original dosing regimen simplifies labeling, and avoids any confusion regarding instructions. Therefore, the revised labeling, and REMS materials accompanying the approval of this efficacy supplement, will include only the proposed dosing regimen and instructions. It should be noted that there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing it from the labeling.

¹⁶Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.

¹⁷Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. *Lancet* 2011; 377: 1155-61.

8. Safety

The safety of the proposed dosing regimen for Mifeprex was supported by the evidence from submitted published literature and postmarketing experience. The focus of the safety analysis was on published studies that evaluated the proposed dosing regimen (Mifeprex 200 mg followed by 800 mcg misoprostol buccally 24-48 hours later), with comparison to the known safety profile of the currently approved dosing regimen.

Exposure: Per the Applicant's submission, the clinical review concluded that there have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000. The clinical review team estimated that exposure to the proposed dosing regimen for their safety analysis was based on approximately 30,000 patients (refer to Table 11 for a list of references used to evaluate safety). Such exposure volume is sufficient to characterize the safety profile of the proposed dosing regimen and other proposed changes in this efficacy supplement.

Deaths: Deaths with medical abortion rarely occur and causality can be difficult to determine. Most of the publications did not specifically report any deaths with medical abortion with Mifeprex. Among the seven U.S. studies submitted to support the safety profile of Mifeprex and misoprostol, only one (Grossman, et al¹⁸) explicitly addressed deaths and noted that there were no deaths among 578 subjects evaluated in the study. Only one observational study (Goldstone, et al¹⁹) from Australia contained a report of a death after a mifepristone and misoprostol dosing regimen. In this retrospective review of 13,345 pregnancy terminations, the authors identified one death from sepsis. The article stated that the death was in an individual who failed to follow-up with her healthcare provider despite showing signs of illness. Based on this information, deaths in association with abortion are extremely rare.

Deaths reported from the postmarketing experience of Mifeprex are summarized below in the Postmarketing Experience section.

Nonfatal serious adverse events: The clinical review team identified key nonfatal serious adverse events (SAEs) associated with the proposed dosing regimen for Mifeprex. These SAEs include: hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. Section 7 of the clinical review dated March 29, 2016, provides a detailed discussion of reported rates of hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. The latter is not an adverse reaction because an ectopic pregnancy would exist prior to the Mifeprex regimen; it represents instead a failure to diagnose an ectopic pregnancy. Overall rates identified by the clinical review team from the published literature are as follows:

- Hospitalization: 0.04-0.6% in U.S. studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women

¹⁸Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.

¹⁹Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. *Med J Austral* 2012; 197: 282-6.

- Serious infection/sepsis: 0-0.2% in U.S. and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in U.S. studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

A study by Upadhyay et al²⁰ reported a 0.31% rate of major complications (including incomplete or failed abortion, hemorrhage, infection or uterine perforation that required hospitalization, surgery or transfusion) for medical abortions (dosing regimen unspecified) through 63 days; this was about double the rate reported for first trimester aspiration abortions and statistically significantly higher. However, these rates were driven by higher rates of incomplete/failed abortion; rates of hemorrhage (0.14%) and infection (0.23%) did not differ from those associated with aspirations.

Only one submitted study reported an ectopic pregnancy. This study (Winikoff et al²¹) reported one ectopic among 847 women (0.12%).

Comment: The proposed dosing regimen has been studied extensively in the literature using U.S. and global sites. Serious adverse events including deaths, hospitalization, serious infections, bleeding requiring transfusion and ectopic pregnancy are rarely reported. The rates of these serious adverse events are well below 1% and do not suggest a safety profile different from the original approved Mifeprex dosing regimen. Although there is less serious adverse event data on women who received Mifeprex and misoprostol between 64-70 days of gestation, the data from a U.S. study of 379 women (Winikoff et al)²² in that gestational age is reassuring that the rates of these serious adverse events are not clinically different from that of other gestational age ranges.

In summary, based on the published literature, nonfatal serious adverse events occur with Mifeprex and misoprostol use with rates generally less than 1%. Increased gestational age (64-70 weeks) was not associated with an increased incidence of nonfatal SAEs. Other submission-specific safety issues that were evaluated including uterine rupture and angioedema/anaphylaxis are discussed in the Postmarketing Experience section below.

Loss to follow-up: The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc et al²³) to 22% in the Grossman et al²⁴ study using telemedicine to deliver medical

²⁰Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. *Obstet Gynecol* 2015;125(1):175-183.

²¹Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008;112(6):1303-1310.

²²Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012;120:1070-6.

²³Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. *Obstet Gynecol* 2014;123:88-95.

²⁴Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.

abortion services.

Comment: Based on these data reviewed by the clinical review team, there is no literature that suggests that follow-up modality alters safety. Therefore, labeling will not be directive regarding follow-up; that will be a decision left to the patient and provider.

Common adverse events: The clinical review team evaluated common adverse reaction data and compared U.S. and global study locations. The comparison revealed that there were differences in the frequency of common adverse reactions, with the reporting rates considerably higher among the U.S. studies. There is no reason to anticipate regional differences in the safety profile for the same treatment regimen, so these differences likely reflect lower ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data in labeling would not be appropriate, as it is unlikely to be informative to the U.S. population of users. The data to be reported in labeling is outlined in Table 1 below:

Table 1: Common Adverse Events ($\geq 15\%$) in U.S. Studies of the Proposed Dosing Regimen

Adverse Reaction	# U.S. 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

Source: Data from Middleton²⁵, Winikoff²⁶ and Winikoff²⁷ as outlined in Table 2 of the CDTL review dated March 29, 2016.

One concerning adverse event is severe vaginal bleeding. Severe vaginal bleeding can result in interventions such as hospitalization and transfusion and may be associated with infection. The overall rate of bleeding across publications varied between 0.5% and 4.2%. Two publications (Sanhueza Smith et al²⁸ and Gatter et al²⁹) evaluated clinically significant bleeding by gestational age. Although the publications reported slightly different rates, there was no trend of increased bleeding requiring intervention with Mifeprex and misoprostol use with increasing gestational age.

²⁵ Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005; 72: 328-32

²⁶ Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

²⁷ Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008; 112(6): 1303-1310

²⁸ Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015;22:75-82.

²⁹ Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

Comment: While not all of the studies reported common adverse events, those that reported did not have unexpected rates of common adverse events. These common adverse events are included in labeling in section 6.1 (Clinical Trial Experience) in the ADVERSE REACTIONS section.

Postmarketing experience – Spontaneous reports:

The safety profile for Mifeprex includes over 15 years of postmarketing safety data available on Mifeprex due to the reporting requirements under the REMS. The Year 3 REMS Assessment report was submitted by the Applicant in June, 2015. The (b) (6) (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. Findings include:

- No Clostridial septic deaths reported in the U.S. since 2009, and none worldwide since 2010.
- The postmarketing rates of hospitalization, severe infection, blood loss requiring transfusion and ectopic pregnancy reported from publications and remain stable and relatively low.

Submission-specific safety issues:

- **Anaphylaxis/angioedema:** The (b) (6) (b) (6) identified a safety signal of anaphylaxis and angioedema with mifepristone administration. This signal was based on a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema. There were no additional cases of anaphylaxis or angioedema identified in the literature.

Comment: (b) (6) and the clinical review team recommended that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling. These labeling sections were discussed with the Applicant and labeling was revised for those sections to describe these serious adverse events.

- **Uterine rupture:** As discussed in the clinical review, the potential risk of uterine rupture was considered because the current labeling for misoprostol includes a Boxed Warning against the use of misoprostol for gestations more than 8 weeks due to the risk of uterine rupture. Although misoprostol is used alone for various obstetric indications, including induction of labor at term, it was important to consider whether labeling about this potential risk is warranted for Mifeprex. Both the clinical reviewer and the (b) (6) (b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports.

Published literature reported three case reports^{30,31,32} of uterine rupture with mifepristone/misoprostol treatment in the first trimester. Of these three reports, two patients had a risk factor for uterine rupture (prior uterine surgery). The third case was in a patient who received more than two doses of misoprostol. After consideration, the clinical review team decided that labeling should include information about this event. The FAERS search did not identify any reports of uterine rupture with use of mifepristone alone. Of 80 reports, 77 cited use of misoprostol alone, and three of mifepristone and misoprostol. Only two reports of uterine rupture in the first trimester were identified, both using misoprostol alone; one entailed an unspecified dose and route of misoprostol at 5 weeks gestation, and one involved vaginal administration of 800 mcg misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar.

Based on the available safety reports of uterine rupture, the review team from (b) (6) and clinical review team concluded that these data demonstrated that uterine rupture with Mifeprex and misoprostol in the first ten weeks (70 days) of gestation is exceedingly uncommon, and occurs most often in the face of a risk factor (previous uterine surgery).

Comment: I agree with the clinical review team and the (b) (6) team that the risk of uterine rupture with first trimester use of mifepristone and misoprostol appears to be extremely rare, and most often associated with a prior uterine scar, a known risk factor for uterine rupture. Labeling of these reports is included in section 2.3 of the DOSAGE AND ADMINISTRATION and section 6.2 of the ADVERSE REACTIONS of labeling to provide additional information to healthcare providers, but no restriction of use is needed based upon this extremely rare adverse reaction.

The clinical review team also evaluated the safety for each of the following major changes proposed in this efficacy supplement:

1. Changing the dosing interval between Mifeprex and misoprostol from 48 hours to 24-48 hours
2. Home administration of misoprostol
3. Use of a repeat dose of misoprostol
4. Change in the follow-up timeframe and method of follow-up
5. Allowing providers other than physicians to provide Mifeprex

³⁰Khan S et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. *Journal of Obstet Gynaecol* 2007; 27: 869-870

³¹ Bika O, Huned D, Jha S, Selby K Uterine rupture following termination of pregnancy in a scarred uterus *J Obstet Gynaecol* 2014; 34(2): 198-9. doi: 10.3109/01443615.2013.841132

³² Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. *BJOG* 2008;15:575-77

To evaluate each of these changes, the reviewers evaluated the adverse event information regarding:

- *Changing the timing interval between Mifeprax and misoprostol and change in the gestational age to 70 days:* Support for the 24-48 hour interval and use up through 70 days was primarily based on a large systematic review by Shaw et al³³. This review evaluated studies looking at different follow-up modalities and demonstrated that there are a variety of acceptable alternatives to in-clinic follow-up that can identify cases in which there is need for additional intervention. In addition, the systematic review did not identify any significant difference in adverse events with different time intervals. Based on these findings, labeling will not be directive regarding specific details of how follow-up should be performed; this will be a decision between the patient and her healthcare provider.
- *Home administration of misoprostol:* The Applicant supplied several published studies that supported this change including Gatter et al³⁴ and Ireland et al³⁵. These studies reported on large numbers of women in the U.S. who took misoprostol at home. The authors showed that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the studies of clinic administration of misoprostol that supported the initial approval in 2000. Given that information is available on approximately 45,000 women from the published literature, half of which incorporated home use of misoprostol, there is no clinical reason to restrict the location in which misoprostol may be taken. Given the fact that the onset of cramping and bleeding occurs rapidly (i.e., generally within 2 hours) after misoprostol dosing, allowing dosing at home increases the chance that the woman will be in an appropriate and safe location when the process begins.
- *Use of a repeat dose of misoprostol:* Safety reporting from studies that evaluated a repeat dose of misoprostol did not specifically assess the subset of women who received a second dose, but no unexpected findings were identified. One randomized controlled trial (Coyaji et al³⁶) conducted in 300 women seeking medical abortion in India looked at a single misoprostol dose as compared to two misoprostol doses. Although there was no difference in the complete pregnancy termination rate in women who received a second misoprostol dose compared to those who did not, the repeat misoprostol dose reduced the need for surgical intervention. This study was reassuring in that there was no significant difference in the adverse events observed—similar percentages of women experienced

³³ Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. *Obstet Gynecol* 2013;121(6):1335-1347.

³⁴ Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

³⁵ Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. *Obstet Gynecol* 2015;126:22-8.

³⁶ Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? *BJOG* 2007;114:271-278.

cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). A supportive systematic review by Gallo et al³⁷ also provided safety information on subjects who received repeat misoprostol. In this review, the only side effects discussed in the trials were diarrhea, which was more common on those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%. Based on these findings, labeling will be changed because the misoprostol dose does not need to be restricted to in clinic administration to assure safe pregnancy termination using the proposed dosing regimen. Given the onset of bleeding and cramping after misoprostol, allowing home administration increases the likelihood that a woman will be in an appropriate and safe location when the pregnancy termination process begins.

- *Change in the follow-up timeframe and method of follow-up:* The Applicant submitted several articles that described different methodologies in follow-up including phone calls and standardized instructions. The clinical reviewers evaluated a study in Scotland by Cameron et al³⁸ that evaluated self-assessment as compared to standard follow-up methodologies (clinic visit or phone call). Most of the women chose self-assessment over an in-clinic visit or phone call, and there were no significant differences in adverse outcomes between women who underwent self-assessment of health compared to those who had a clinic visit or phone call. Among women with an ongoing pregnancy after Mifeprex and misoprostol, the majority self-identified and presented within two-weeks for care. Based on this information and the other data from the Raymond systematic article³⁹ that did not identify a difference in failure rate for earlier (less than one week) as compared to one week or greater of follow-up, sufficient support was provided to use a broadened window of 7 to 14 days for follow-up. This revised follow-up time frame will be included in labeling.
- *Allowing providers other than physicians to provide Mifeprex:* The current Prescriber's Agreement in the REMS specifies that "...Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications..." In addition, current labeling states that Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. However, labeling states that other healthcare providers, acting under the supervision of a qualified physician, may also provide Mifeprex to patients. Several published studies submitted by the Applicant indicate that health care providers such as nurse practitioners, nurse midwives, and physician assistants are

³⁷ Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. *Contraception* 2006;74:36-41.

³⁸ Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? *Contraception* 2015;91:6-11.

³⁹ Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

currently providing abortion services. One of these studies (Kopp Kallner et al⁴⁰) was a randomized controlled trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. Success rates were $\geq 96\%$ regardless of gestational age. The nurse midwife group had few complications, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, $p=0.14$). No serious complications were reported and no blood transfusions were administered in the study. Based on this and other supportive studies, the information supports the efficacy and safety of allowing healthcare providers other than physicians can effectively and safely provide abortion services, provided that they meet the requirements for certification described in the REMS. The clinical team also felt that the term “healthcare provider who prescribes” would be the appropriate terminology as prescribing ability is a critical factor in dispensing Mifeprex.

The clinical review team concluded that the evidence demonstrated acceptable safety for each of the above proposed changes, and I concur with their conclusion. The proposed dosing regimen has a similar safety profile as the original regimen approved in 2000. Adverse outcomes of interest, such as deaths, serious infection, transfusions, ectopic pregnancies and uterine rupture, remain rare, and are not necessarily attributable to Mifeprex use. Overall, the rate of deaths and nonfatal serious adverse events are acceptably low, and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen. No association between adverse outcomes and increasing gestational age was identified. Finally, the available information supports the safety of the other proposed changes, including increasing the flexibility of the time interval between Mifeprex and misoprostol, at home use of misoprostol, use of a repeat dose of misoprostol, change in the follow-up timeframe and allowing health care providers other than physicians to prescribe and dispense Mifeprex were acceptable.

9. Advisory Committee Meeting

Mifeprex is not a new molecular entity requiring discussion before an advisory committee. In addition, an advisory committee was not necessary as the application did not raise complex scientific or other issues that would warrant holding an AC before approval.

10. Pediatrics

This efficacy supplement triggered requirements under the Pediatric Research Equity Act (PREA). The Agency granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarcheal females.

⁴⁰ Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. *Human Reprod* 2010;25(5):1153-1157.

The Applicant fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old. Efficacy and safety information in these adolescents was based on a U.S. study in 322 postmenarcheal adolescents (Gatter et al⁴¹). Of the 322 adolescents, 106 of these adolescents were under 16; see Table 2 below:

Table 2: Age and Number of Adolescents Undergoing Medical Abortion (Gatter et al⁴²)

Age of Subject	Number of Subjects evaluated
11	1
12	1
13	2
14	20
15	82
16	216

Source: Refer to Table 17 of the Medical Officer's review dated March 29, 2016

The Gatter et al⁴³ study reported that postmenarchal females less than 18 years old had a 98.7% pregnancy termination rate as compared to females aged 18-24, who had a rate of 98.1%. This article reported that loss to follow-up was slightly higher in those less than 18 years old, however, age did not adversely impact efficacy outcomes.

One issue was whether adolescents would comply with at home use of misoprostol. The Gatter⁴⁴ et al study incorporated at home use of misoprostol into the Mifeprex dose regimen given to all females, including postmenarchal females less than 18 years old. The overall efficacy in adolescents was similar to that of all older women. This information supports at home administration of misoprostol in postmenarchal females under 17.

Two other published studies provided additional efficacy on Mifeprex use by adolescents for pregnancy termination:

- Phelps et al⁴⁵ evaluated data from 28 adolescents aged 14 to 17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. In this study, 100% of subjects had a complete pregnancy termination, with five not requiring misoprostol.

⁴¹Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

⁴² Ibid.

⁴³Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

⁴⁴Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

⁴⁵Phelps RH, et al. Mifepristone abortion in minors. *Contraception* 2001;64:339-343.

- Niinimaki et al⁴⁶ used data from a Finnish Registry from 2000-2006. An analysis of efficacy between adolescents under age 18 compared to the women \geq age 18 indicated that the adolescent group had a lower rate of incomplete abortions as compared to adults. And efficacy outcomes in adolescents were similar to those of adult women.

The safety of Mifeprex in postmenarcheal adolescents was primarily supported by adverse event information from the Gatter et al⁴⁷ study. (b) (6), (b) (4)

Supportive data from a Finnish registry (Niinimaki et al) from 3024 adolescent females under 18 years of age reported that, compared to adult women, the risks of hemorrhage (adjusted odds ratio 0.87 [95% confidence interval: 0.77 to 0.99]), incomplete abortion (0.69, [95% confidence interval: 0.59 to 0.82]), and surgical evacuation (0.78, [95% confidence interval: 0.67 to 0.90]) were lower in the adolescent cohort. In the Finnish registry study, a majority of adolescents and adults received both Mifeprex and misoprostol. Safety findings from the Gatter et al and Niinimaki et al studies are reassuring and indicate that the safety profile of Mifeprex is similar between postmenarcheal adolescents and adult women.

Additional details from this article and other published data on Mifeprex use in adolescents (females under 17) are described in the clinical review (Refer to the Medical Officer's review dated March 29, 2016).

(b) (6) concurred that the efficacy and safety data in postmenarcheal adolescents less than 17 years old was sufficient to support the use of Mifeprex in this pediatric population and to fulfill the PREA pediatric study requirement. The revised Mifeprex labeling will state that that efficacy and safety are similar to adult women in the Pediatric Use section (8.4).

11. Other Relevant Regulatory Issues

(b) (6)

(b) (6) reviewed the Medication Guide in conjunction with the (b) (6) (b) (6). Both (b) (6) and (b) (6) found the Medication Guide to be acceptable with recommended changes (See review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in

⁴⁶Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

⁴⁷Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

⁴⁸Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

the Medication Guide and incorporated appropriate changes into the final agreed upon Medication Guide.

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

(b) (6) reviewed the Prescribing Information (PI) in addition to the joint review with (b) (6) of the Medication Guide in conjunction with (b) (6). After review, (b) (6) provided recommended changes (See (b) (6) review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in the PI and incorporated appropriate changes into the final label.

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

(b) (6) (b) (6) in the (b) (6) (b) (6) reviewed the proposed modifications to the REMS. The (b) (6) review reflected agreement with the Applicant's proposed REMS changes which include:

- Removal of the term “under Federal law” from the Prescriber’s Agreement.
- Replacement of the word “physician” with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex. (b) (6) believes that the Applicant’s proposed terminology of “(b) (4)” is too broad and that a more appropriate description is “healthcare provider who prescribes,” which limits acceptable healthcare providers to those who are licensed in their state to prescribe medications.
- Removal of the Medication Guide from the REMS. The Medication Guide remains an important education tool for patients. It will still be dispensed to each patient in accordance with 21 CFR part 208. As described in the Medication Guide Guidance, a Medication Guide is not necessary to ensure that the benefits outweigh the risks of Mifeprex
- Modification of Element to Assure Safe Use (ETASU) A, the Prescriber’s Agreement. (b) (6) recommends changing the name of the document to the Prescriber’s Agreement Form to be consistent with other REMS programs. References to “physician” should be changed to “healthcare provider who prescribes.”
- (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
 1. The established safety profile over 15 years of experience with Mifeprex is well-characterized, stable, and known serious risks occur rarely
 2. The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208
 3. The Prescriber’s Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have
 4. Established clinical practice provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment. FDA has removed REMS

requirements in other programs based on the integration of the REMS safe use condition into clinical practice.

Other revisions to the REMS document will be made for consistency with changes described above and to reflect current FDA thinking and practice regarding format, language and flow in REMS documents. These changes include modification of the Mifeprex REMS goal, changes in requirements to certify prescribers (removal of the requirement to obtain a Patient Agreement) and other minor edits.

In summary, the overall (b) (6) recommendation for the REMS modification for this efficacy supplement was approval (Refer to (b) (6) review dated March 29, 2016).

12. Labeling

Carton and container labeling was reviewed by the (b) (6) (b) (6) (b) (6) and the (b) (6) (b) (6) (b) (6) (b) (6) Their comments were conveyed to the Applicant as appropriate.

The label was submitted in the format prescribed by the PLR. Although the supplement was submitted prior to when it would otherwise have been required to comply with the PLLR requirements, the review team believed it would be of value to harmonize with this labeling standard to the extent possible.

Specific issues discussed during labeling negotiations included the selection of studies for inclusion in Section 6.1 (Clinical Trial Experience in the ADVERSE REACTIONS section) and 14 (CLINICAL STUDIES section). Only studies that evaluated the specific proposed regimen were included in these sections. For the Adverse Reactions section, examination of the common adverse reaction data by U.S. compared to non-U.S. study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the U.S. studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data would not be appropriate, as it is unlikely to be informative to the U.S. population of users. In the case of serious adverse reactions, the reported frequency was quite similar regardless of study location; for this reason, serious adverse reaction information from global studies is reported. Agreement on labeling was reached on March 29, 2016.

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

Postmarketing Requirements/Postmarketing Commitments: None.

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

The teams determined that the following REMS modifications were warranted:

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

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

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

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

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

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

APPEARS THIS WAY ON ORIGINAL

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

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

13. Decision/Action/Risk Benefit Assessment

Decision:

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

Benefit Risk Assessment:

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

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

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

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

1. The Medication Guide can be removed from the Mifeprex REMS program. The Medication Guide requirements under 21 CFR part 208 require the Medication Guide to be distributed to patients. Mifeprex will only be dispensed by a healthcare professional who will be knowledgeable and able to provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or follow-up that may be required as appropriate, and who will answer any questions the patient may have. In that setting, the Medication Guide will already be a required available tool for counseling. Therefore, given the existing requirements under 21 CFR part 208, I concur that there is no reason for the Medication Guide to specifically be a part of the REMS.
2. The Prescriber Agreement Form (ETASU A) as revised reflects current FDA format and content to conform to current REMS programs and reflect the labeling changes that will be approved in this supplement. I concur that the changes are acceptable.
3. Revision of the Mifeprex REMS goals (ETASU C) will adequately mitigate the risk of serious complications by requiring certification of healthcare providers who prescribe and ensuring the Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber.
4. Removal of the Patient Agreement Form (ETASU D): I concur with the clinical review team that the Patient Agreement Form, which requires a patient's signature, does not add to safe use conditions for the patient for this REMS and is a burden for patients. It is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent. The Patient Agreement Form contains duplicative information already provided by each healthcare provider or clinic. I believe that it is much more critical for the healthcare provider who orders or prescribes Mifeprex to provide and discuss informed consent derived from their own practice so that care can be individualized for the patient.

I support that the Mifeprex REMS with ETASUs A and C remain in place to support conditions critical to the use of the drug. Therefore, the implementation system and timetable for assessments should continue.

I also agree with the clinical review team that the reporting requirements should only be required for deaths. It is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends. However, after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged. Therefore, I agree that reporting of labeled serious adverse events other than deaths can be collected in the periodic safety update reports and annual reports to the Agency.

In summary, I believe that the benefit-risk profile for Mifeprex continues to be favorable and with the agreed-to labeling changes and REMS modifications, the Mifeprex REMS program will continue to assure safe use. Therefore, I support approval of this efficacy supplement and REMS modifications.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked (b) (6) and the (b) (6) (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 the (b) (6) (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.

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/s/

(b) (6)

03/29/2016

EXHIBIT G

**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:

[Redacted] (b) (6)

TO:

[Redacted] (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, [Redacted] (b) (6)

[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 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] (b) (6) and [Redacted] (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 (b) (6) (b) (6) Review of the Year 4 Risk Evaluation and Mitigation Strategy (REMS) assessment report that relate to an unapproved dosing regimen for Mifeprax.¹

Mifeprax (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 Mifeprax 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 (b) (6) REMS assessment reviewer had noted that there was use of the unapproved dosing regimen of Mifeprax 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 Mifeprax. 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 (b) (4) 70 days). This supplement was under review at the time the October 2015 (b) (6) REMS Assessment review was conducted.

The (b) (6) (b) (6) is reviewing Danco's efficacy prior approval supplement-020 (PAS-020) to determine whether the supplement can be approved. Because (b) (6) review encompasses all of the data and information submitted in the supplement, (b) (6) defers to (b) (6) with respect to the safety and efficacy of the dose and dosing regimen proposed by Danco.

¹ (b) (6) (b) (6) Review of Year 4 Risk Evaluation and Mitigation Strategy (REMS) Assessment Report, dated October 13, 2015

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(b) (6)

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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 REMS¹

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.

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 [REDACTED] (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 [REDACTED] (b) (6) and [REDACTED] (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 [REDACTED] (b) (4), [REDACTED] (b) (6) the Director, OSE, and [REDACTED] (b) (6), to the Directors of [REDACTED] (u) (u) and [REDACTED] (u) (u). 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 [REDACTED] (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)

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

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 (b) (6) and they are in agreement.

2. (b) (6) 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 (b) (6) 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) (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 (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.

(b) (6) (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, (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 (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 (b) (4) were rejected by (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, (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

PRESCRIBER AGREEMENT FORM

Mifeprex[®] (Mifepristone)
Tablets, 200 mg

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.



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

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

03/2016

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.



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.

PATIENT AGREEMENT FORM



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.

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

/s/

[Redacted] (b) (6)
03/29/2016

[Redacted] (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

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1. INTRODUCTION

This review provides the (b) (6) (b) (6) evaluation of the modifications to the risk evaluation and mitigation strategy (REMS) for Mifeprax 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

Mifeprax is a synthetic steroid with antiprogesterational 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. Mifeprax was approved September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (Subpart H).² Mifeprax 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, 2011 with 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 Mifeprax REMS

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

¹ (b) (6)

² NDA approval letter Mifeprax (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:

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.

/s/

(b) (6)

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