Exhibit 1

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

Alliance for Hippocratic Medicine, *et al.* Plaintiffs, v. U.S. Food and Drug Administration, *et al.*, Defendants.	Case No. 2:22-cv-00223-Z

DECLARATION OF NOAH T. KATZEN

Pursuant to 28 U.S.C. § 1746, I, Noah T. Katzen, hereby declare:

1. I am an attorney in the U.S. Department of Justice, Civil Division, Consumer Protection Branch. I am assigned to represent Defendants in the above-captioned case. The statements made herein are based on my personal knowledge, and on information made available to me in the course of my duties and responsibilities as Government counsel in this case.

2. I submit this declaration in support of Defendants' Opposition to Plaintiffs' Motion for a Preliminary Injunction.

3. Filed herewith as Exhibits 1A-1E are true and correct copies of the following documents that I downloaded from the indicated websites:

Exhibit No.	Exhibit Name
1A	CDER, Clinical Review (Mar. 29, 2016), https://perma.cc/SR23-X9LJ (last visited Jan. 13, 2023)
1B	CDER, Cross Discipline Team Leader Review (Mar. 29, 2016), https://perma.cc/5KSW-Q6AF (last visited Jan. 13, 2023)
1C	OLC, *Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions* (Dec. 23, 2022), https://perma.cc/8XHW-32JD (last visited Jan. 13, 2023)
1D	Mifeprex (mifepristone) Prescribing and Label Information, https://perma.cc/2UJ5-8WVF (last visited Jan. 13, 2023)

1E	CDER, Medical Officer's Review of Amendments 024 and 033 (Nov. 22, 1999), https://perma.cc/K69R-33EZ (Part 1) (last visited Jan. 13, 2023) and https://perma.cc/RZ2M-9DQH (Part 2) (last visited Jan. 13, 2023)

I swear under penalty of perjury that the foregoing is true and correct. Executed on January 13, 2023.

/s/ Noah T. Katzen
NOAH T. KATZEN

Counsel for Defendants

Exhibit 1A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

MEDICAL REVIEW(S)

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.

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:

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:

- 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.

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.

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues with Consideration to Related Drugs

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

Reviewer comment:

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

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

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

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

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

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 globally[4]; 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.

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

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

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

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

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

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

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

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

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

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

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 Mifeprex 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.

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.

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 Mifeprex®. 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}) (± standard error) = 1.77 (±0.23) mg/L, the mean time to reach C_{max} (T_{max}) = 0.81 (±0.16) hour, and the mean area-under-the curve (AUC) = 25.8 (±2.2) mg·h/L. While the effects of sex on the disposition of mifepristone have not been evaluated using Mifeprex®, 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

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 Mifeprex®. 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 Mifeprex® 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 Mifeprex® 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.

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 Bulletin[1]). 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.

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

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.

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)	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

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 review[12] 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 review[18] 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.

- Efficacy outcomes do not appear to be related to other baseline characteristics including age, race, body weight, gravidity and previous spontaneous abortions. (Spitz data[26] and many subsequent studies)
- Data from the original US trial (1994-95; Spitz 1998[26]) 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 review[18]) 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 2012[19]); 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)
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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).

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**

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."

(b) (4)

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

Reviewer's comment:

The 2009 Fjerstad article[28] 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 Mifeprex 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 Mifeprex 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 MAB[30] 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

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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.

> 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, Spitz[31] 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 Federation[32], 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]

<u>European practice</u>:

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.

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 Gynecologists[34], 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.

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. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.

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. Intnational 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

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 review[18] 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 study[45] 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

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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.

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 trial[31] 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).

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

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.

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.

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.

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.

[Y]The 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

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 PPFA approved medical abortion through 70 days, so this is currently their standard of care.

Reviewer's Final Recommendation:

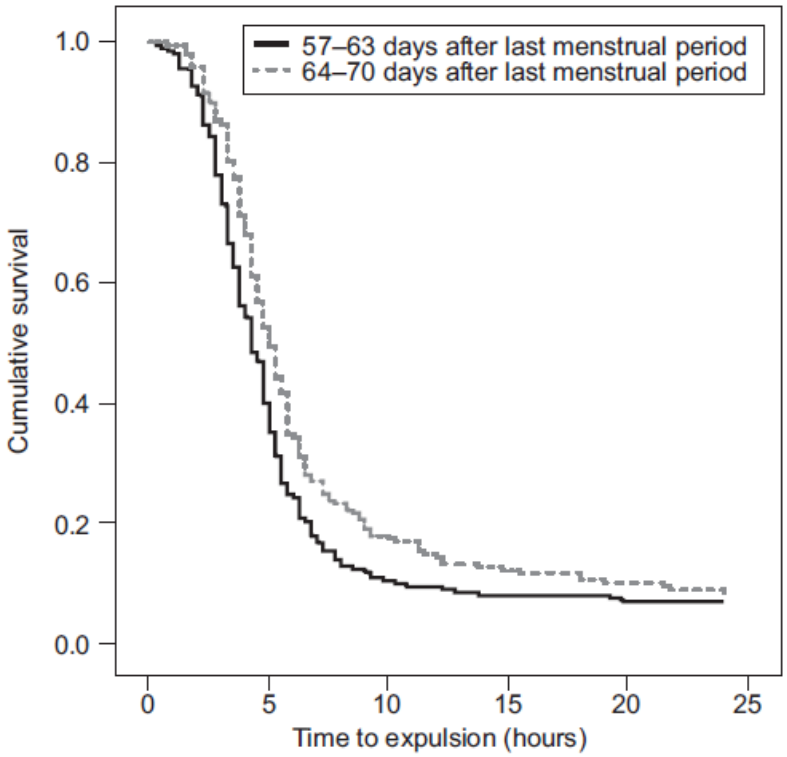
The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved for use through 70 days gestation (10 weeks from the first day of the LMP).

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.



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.

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 home 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

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) review[18] 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 misoprostol[19], 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

studies report specific outcomes. The Chen and Creinin 2015 review[12] 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 2nd Dose	Success with 2nd 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.**

[Y]These 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.

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:

- Olavarietta[85] demonstrated efficacy of 97.9% when the MAB was provided by nurses as compared with 98.4% with physicians
- Kopp Kallner[84] showed efficacy of 99% with certified nurse midwives versus 97.4% with physicians
- Warriner[52] demonstrated efficacy of 97.4% with nurses versus 96.3% with physicians
- Puri[83] 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.

"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 review[18] 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 article[18] 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

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 study[26] 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 (Raymond[18].

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. 2001[53] 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.

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 study[20], 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.

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.

- 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

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.

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 (Gatter[13] and Ireland[15]) 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

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, 2011[36]) and noted zero deaths among 578 subjects. Among the three international studies, only one[20] 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

from 0.003-1.1%. Only three articles separated out hospitalizations by gestational age. In Gatter 2015[13], there were 3/8495 hospitalizations among women ≤ 49 days, 3/3142 among women at 50-56 days gestation and none among women at 57-63 days. In Winikoff 2012[19], there were only two hospitalizations, both among women at 57-63 days, and none in the 64-70 days gestation group. In Creinin[25] 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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Table 12: Hospitalizations by Gestational Age

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 2015[13], the two serious infections were in women ≤ 49 days gestation. There were no serious infections in

women at 50-56 or 57-63 days gestation. In Winikoff 2012[19], 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 2015[13], 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 2012[19], there were: two in the 57-63 days group

and 1 in the 64-70 days group. In Creinin 2007[25], there were two women transfused each in the 50-56 days and 57-63 days. Only one international study[20] (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 2015[13]	retrospective	13,373	4 (0.03%)	N=8945 1 (0.01%)	N=3142 3 (0.1%)	N=1286 0	N/A
Chong 2015[17]	prospective	400	NR	NR	NR	NR	N/A
Winikoff 2012[19]	prospective	729	3 (0.41%)	N/A	N/A	N=325 2 (0.53%)	N=304 1 (0.29%)
Grossman 2011[36]	prospective	578	1 (0.17%)	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	4(0.7%)	N=229 0	N=172 2 (0.36%)	N=145 2 (0.36%)	N/A
Middleton 2005[24]	prospective	223	1 (0.45%)	NR	NR	N/A	N/A
International							
Ngoc 2014[16] Vietnam	prospective	1433	NR	NR	NR	NR	N/A
Goldstone 2012[20] Australia	retrospective	13,345	11 (0.08%)	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.

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 2008[23].

Several studies also included less detailed, though still useful, information on adverse events. Ireland et al[15] conducted a retrospective review of 30,146 women undergoing

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, Grossman[36] 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 al[55] 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.

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 2014[16]) to 22% in the Grossman[36] 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 2015[13] 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 study[22] 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 2012[19] 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

(b) (6) conducted separate literature searches on this topic. Chen et al 2008[56] 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 al[57] 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.

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

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.

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 al[26], 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. Gatter[13] and Ireland[15] 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 (2012[19] and 2008[23]), Grossman[36], Creinin[25] and Middleton[24] reported on smaller numbers of US subjects. Internationally, Goldstone[20] reported on 13,345 medical abortions, while Kopp Kallner[64], Løkeland[65], Chong (2012)[40], Bracken[49], Pena[44],

[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.

Ngoc[16], Louie[14], Sanhueza Smith[48], Boersma[22] and Lynd[66] 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 al[50] 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 Chong[67], 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.

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 al[68] 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).

Gallo[69] 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.

used. In a study by Blum et al[70], 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.

abortion. Grossman and Grindlay[71] 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 ≥90% and negative predictive values (NPVs) ≥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) ≤33%."

This reviewer analyzed relevant studies that were submitted by the Applicant and referenced in the Grossman and Grindlay assessment.[71] Perriera et al[21] 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 al[72] 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;

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 al[66] 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 al[73] 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 has 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.

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 Bulletin[1] 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

- 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 inTable 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 2005[24], which includes subject to 56 days, and Sanhueza Smith 2015[48] and Winikoff 2012[19], 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

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 ≤ 56 days, 4.2% (8/190) in women 57-63 days and 1.4% (2/148) in women 64-70 days. In Gatter 2015[13], 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.

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 2012[19] 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.

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-Uclef in France in 1989.[76] A prospective observational study[77] from fifteen French pharmacovigilance centers followed women exposed to mifepristone in the first trimester between1997 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.

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.

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 al[54] 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

adolescents and 24,006 adult women undergoing medical abortion (regimen unspecified). The study population included women ≤ 20 week's gestation; 84.6% of the adolescents were ≤ 12 weeks, while 86.6% of the adults were ≤ 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).

Phelps[53] had previously 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. 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 Gatter[13] 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 Goldstone[20] 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. Ngoc[16] is based in Vietnam and Cameron[73] is based in Scotland, while Gatter[13] and Horning[78], 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.

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.

which labeling is based (Spitz, 1998[26]), 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, Lohr[79] 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. Creinin[25] 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 study[80] 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) 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.

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 Renner[82] 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 al[83] 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 Kallner[84] 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.

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%). Olavarrieta[85] 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, Bousieguez 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.

representation of the varied practitioners who are prescribers, while at the same time using language that is consistent with statute. We concur with the (b) (6) 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

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

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

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:

> **"Mifeprex 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 Mifeprex 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 Mifeprex.

8 Postmarket Experience

A comprehensive review of the adverse events associated with Mifeprex 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

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)

† 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.

(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.

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 REMS[86] under section

86 Federal Register / Vol. 73, No. 60 | Issued: March 27, 2008

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)

- 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) 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.

APPEARS THIS WAY ON ORIGINAL

[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.

- 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

9.5 List of References

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9.6 Mifepristone Approvals Globally

1988
- China
- France

1991-
- UK

1992
- Sweden

1999
- Austria
- Belgium
- Denmark
- Finland
- Germany
- Greece
- Iceland
- Israel
- Luxembourg
- Netherlands
- Russia
- Spain
- Switzerland

2000
- Norway
- Taiwan
- Tunisia
- US

2001
- New Zealand
- South Africa
- Ukraine

2002
- Belarus
- Georgia
- India
- Latvia
- Serbia
- Vietnam

2003
- **Estonia**

2004
- Guyana
- Moldova

2005
- Albania
- Hungary
- Mongolia
- Uzbekistan

2006
- Kazakhstan

2007
- Armenia
- Kyrgyzstan
- Portugal
- Tajikistan

2008
- Nepal
- Romania

2009
- Cambodia
- Italy

2010
- Zambia

2011
- Ghana
- Mexico
- Mozambique

2012
- Australia
- Bangladesh
- Ethiopia
- Kenya

2013
- Azerbaijan
- Bulgaria
- Czech Republic
- Slovenia
- Uganda
- Uruguay

2014
- Thailand

2015
- Canada

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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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03/29/2016

I concur with (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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					on both the approved product and the proposed regimen.
15.	Describe the scientific bridge (e.g., BA/BE studies)	x			See #14.
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Many articles from the published medical literature. Study Title: Sample Size: Arms: Location in submission:	x			
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	x			The applicant provides 54 articles total, with 32 specifically on efficacy of the proposed regimen. These include controlled trials, meta-analyses, observational and retrospective studies.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	The applicant provides 54 articles total. 46 are studies (trials, retrospective, observational studies) and of these 17 are foreign. There are also 3 metanalyses which include foreign studies.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			The applicant provides 21 articles with information on safety, specifically on the serious adverse events of interest (hospitalization,

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 arythmogenic 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).

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	

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.

(b) (6)

Reviewing Medical Officers — Date: 7/16/15

(b) (6)

Date: 7/16/15

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)

07/16/2015

(b) (6)

07/17/2015

(b) (6)

07/17/2015

Exhibit 1B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

CROSS DISCIPLINE TEAM LEADER REVIEW

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:	***Approval***

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

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, provider 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.

- 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, 2011with 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) 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:

"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 Mifeprex 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.

(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 2006[1] 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 2005[2] 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 2005[3] 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.

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[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

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 [redacted] provided recommendations to [redacted] based on its review of the proposed modifications to the REMS. In the [redacted] review dated March 29, 2016, the primary reviewer, [redacted] indicated [redacted] 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; [redacted] believes that the Applicant's proposed terminology of "[redacted] 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 [redacted] and [redacted] considered the recent REMS Assessment data submitted by the Applicant in June 2015, postmarketing summary reporting by the [redacted] 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, [redacted] 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. [redacted] 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. [redacted] 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

- 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) (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)

   d. Provide for a repeat dose of misoprostol if complete expulsion has not occurred by follow-up

2. Change in gestational age through which Mifeprex may be used from 49 to 70 days [redacted (b) (4)])
3. Change labeling regarding follow-up from specifying an in-office assessment on Day 14 to advising that patients should follow-up with their healthcare provider approximately 7-14 days after taking Mifeprex, and not specifying what assessment(s) should be performed
4. Change in labeling and REMS statements that currently provide for Mifeprex only to be supplied to, prescribed by, and administered by or under the supervision of a physician
5. Change labeling re: description of time to expulsion from 4-24 hours to 2-24 hours
6. Add misoprostol in the indication statement ("Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days' gestation.")
7. Remove the term "Under Federal law" from Prescriber's Agreement
8. Address the Pediatric Research Equity Act (PREA) requirements for pediatric studies by requesting a partial waiver in females under the age of 12 (because pregnancy does not occur in premenarcheal females) and by extrapolation from adult data bolstered by data from females under age 17
9. The Applicant also proposed conforming revisions to REMS documents based on changes requested above

Table 4 in the Appendix presents a summary of the major publications submitted and reviewed in support of the supplement. Because each publication contributes some safety and/or efficacy data for consideration of one or more given topics, this review will not follow the usual practice of discussing safety and efficacy separately, but will provide a topic-centered discussion of the totality of the data.

Certain changes (6 and 7 above) entail regulatory decisions that are not based upon review of data; these are discussed in Section 7.7. Other changes, necessitated by compliance with current labeling standards such as the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR), are discussed in Section 12.

The original approval of Mifeprex was based on data from one US trial and two French trials. The US data included 827 women with gestations $\leq$ 49 days, and showed a 92.1% success rate, with success defined as complete expulsion of products of conception (POC) without need for surgical intervention. Of cases that did receive surgical intervention, 1% had ongoing pregnancies, while 4.7% had incomplete abortions (pregnancy terminated, but POC not completely expelled). The French studies included 1,681 women and showed overall success in 95.5% of women, with 1.3% having ongoing pregnancy and 2.9% receiving surgical intervention for incomplete abortion.

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 2012[4], Boersma[5], Sanhueza Smith[6]) and one randomized controlled trial (RCT) (Olavarrieta[7]) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin[8] 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, Bousieguez 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

gestation; these are discussed in Section 7.3. The large systematic review[8] 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 2008[9]) 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 2012[10]), while Middleton[3] 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 review[11] of global studies included over 45,500 women, of whom 2,200 received misoprostol doses ≥ 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 (Gatter[12]) 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 2012[13]) reported rates of known/suspected infection of 0.23%, and of hemorrhage of 0.1%. Finally, a study (Ireland[14]) 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 Raymond[11] 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

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 Kulier[15] 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. Raghavan[16] 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.**
- (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 Wedisinghe[17], which identified five RCTs, four of which used the proposed dose (Creinin 2004[18], Creinin 2007[19], Guest 2007[20]

[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 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

[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

and Schaff 2000[21]), 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 Mifeprex 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 review[8] 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 Mifeprex, 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 Mifeprex 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

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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

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 review[11] 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 Reeves[22] reports that fewer than 5% of women taking Mifeprex and vaginal misoprostol will have a persistent gestational sac one week after using Mifeprex, 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 Reeves[22] publication pooled data from two RCTs (Creinin 2004[18] and 2007[19]) in which women who had not expelled the gestational sac per a sonographic assessment 6-11 days after taking Mifeprex 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 201[24] – 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

- Chen and Creinin 2015[8] – 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 2015[5] – 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 2014[23] – 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 2012[10] – 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 2008[9] – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%

Three other studies (Bracken 2014[24], Coyaji 2007[25], and Raghavan 2011[16]) 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 2006[26] 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

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 143[27]) 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 ≤ 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 2012[4], Boersma[5] , Sanhueza Smith[6]) evaluating efficacy by gestational age, rates for 64-70 days were 91.2, 92.8 and 96.2%, respectively.
- The fourth study (Olavieretta[7]) 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 Creinin[8]) provided a pooled success rate for 64-70 days of 93.1%; a total of 33,846 women were ≤ 70 days.
- Another systematic review (Abbas[28]) 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 (Gouk[29]) 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

- One (Bracken[24]) 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 dosing[2], 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 review[11] 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.

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

Team Leader Comments:

- **The Raymond analysis[11] 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 2015[7], Kopp Kallner 2015[30] and Warriner 2011[31]) and one comparative study (Puri 2015[32]) 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 (Olavarrieta[7]).

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[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

Team Leader Comments:

- **The available data support the safety and efficacy of allowing certain non-physician healthcare providers to order, dispense and administer Mifeprex, 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) (6) 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 2012[4] 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 (Lohr[33] [which administered misoprostol 5 minutes after Mifeprex], Creinin 2004[18] and 2007[19] [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 Mifeprex labeling currently states in the indication statement of the Indication and Use (I&U) section:

> Mifeprex 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

> 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

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 study[12], 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 information[34] 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 2011[35] 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

2012[13]) 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 Mifeprex 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 Mifeprex 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

Upadhyay[36] 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

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 Middleton[3], Winikoff[4] and Winikoff[9]

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).

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

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

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.

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) [redacted]. 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.

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

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 trigged 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, Gatter[12] 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. Upadhyay[36] 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 (Gatter[12], Cameron[40, 41], Ngoc[42], Horning[43]), 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

85.1%. Thus, it does not appear that there is any meaningful difference based on age in a postmenarcheal female's ability to comply with the dosing regimen and follow-up.

(b) (6) agreed to a partial waiver for patients from birth to 11 years of age, and concurred that adequate data are available for postmenarchal adolescents.

11. Other Relevant Regulatory Issues

Because this efficacy supplement is based on published literature, no consult was made to the (b) (6)

12. Labeling

Carton and container labeling was reviewed by the (b) (6) ((b) (6) the (b) (6) ((b) (6) and the (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 and 14. 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 US vs. non-US study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the US studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-US studies. Regardless, inclusion of this non-US data would not be appropriate, as it is unlikely to be informative to the US 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.

13. Recommendations/Risk Benefit Assessment

13.1 RECOMMENDED REGULATORY ACTION

I recommend that the Mifeprex efficacy supplement receive an Approval action.

13.2 RISK BENEFIT ASSESSMENT

The data reviewed in support of the changes proposed in this efficacy supplement confirm that the Mifeprex regimen as revised is safe and effective for termination of intrauterine pregnancy through 70 days gestation; for this reason, I believe that the benefit/risk profile of Mifeprex is favorable. (b) (6) and (b) (6) continue to recommend a REMS for this product, but agree that the experience over the past 16 years demonstrates that certain elements of the REMS may be modified or eliminated, as detailed below.

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 (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 findi
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	2nd 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: (Hospitalizatio 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 1st dose		Regimen, *GA*	Total: 97.7% ≤ 49: 97.8% 50-63: 93.7% 64-70: 96.2% Total ongoing preg: 0.7%	Hospitalizatio
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 g hosp for bleed underwent SA No transfusio Hospitalizatio
Sanhueza Smith 2015 Mexico	Observational	1,001 (≤ 56 days: 622 57-63 days: 196 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 r described

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 findi
		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 Transfusions 0.6% Hospitalizatio 0.9% Buccal vs. ora ↓nausea, ↑dia fever, dizzines
						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	
						2nd 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	Hospitalizatio 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 needi aspiration ↑ at higher GA

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 findi
							36-42: 98..8% 43-49: 98.1% 50-56: 96.9% 57-63: 95.5% Total ongoing preg: 0.5%	Infx req'g hospitalizatio 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 hospitalizatio transfusion 0.
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2nd dose of miso allowed for incomplete Ab		Regimen, MAB vs. SAB *(additional dose, home miso)*	MAB 99.6% SAB 99.8%	Hospitalizatio visit, uterine perforation, infection, transfusion – in total, NS di
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

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 findi
							pregnancy at tx)	
Blum, Raghavan et al. 2012 Tunesia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			Regimen, *home miso* *GA*	Total: 92.9% *≤ 49: 96.3%* *50-56: 86.5%* *57-63: 96.3%*	Serious AEs r discussed
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 ex chills sig high 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 *GA* *2nd dose of miso*	Total: 96.4% (Either dose) *≤ 42: 95.8%* *43-49: 96.2%* *50-56: 98.5%* *57-63: 93.0%* *92% success*	↑ AEs in 800 a Vomiting 22% Fever/chills 3
Giri 2011 Nepal	Prospective	100	63 days			Regimen	Total 93.6%	No transfusio hospitalizatio
Goldstone 2012 Australia	Retro observational	13,345	63 days			Regimen, *home miso*	96.5% Ongoing preg: 0.6%	1 death from s (<0.01%) Infection w/o 0.2% Hemorrhage 0 Transfusion 0
Louie 2014 Azerbaijan	Observational	863	63 days			Regimen, Home miso	92% selected home misoprostol; overall success	Common AEs reported

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 findi
							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, *follow-up***	**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:**	

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 findi
		≤ 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	2nd 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 2nd miso dose)	Higher rates o nausea, diarrh warmth/chills immediate mis SAEs: transfu 0.4% (all in 24 group); acute infx, treated a 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 2nd miso dose)	Side effects d the interval b/ and miso were higher in the 2 hr group; rate nausea & vom after miso dos 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):*	

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 findi
		≤ 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 ((only in 6-8 hr group)
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) *GA*	Buccal: 97.1% *Buccal:* *≤ 49: 96.6%* *50-63: 100%*	No hospitaliza Common AEs reported
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: (
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

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 findi
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 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 mi Similar rates c common AEs diarrhea sig. r 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 ↑	

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 findi
							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	2nd 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: Hospitalizatio 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 hospitalizatio transfusion 0.
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2nd dose of miso allowed for incomplete Ab		*Regimen, MAB vs. SAB (additional dose,* home miso)	MAB 99.6% SAB 99.8%	Hospitalizatio visit, uterine perforation, infection, transfusion – in total, NS di
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

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 findi
						GA	***Buccal:*** ***≤ 42: 98.7%*** ***43-49: 96.4%*** ***50-56: 95.7%*** ***57-63: 94.8%***	
Blum, Raghavan et al. 2012 Tunesia & Vietnam	**DB RCT, placebo control**	**441 (220 mife/miso, 221 miso only)**	**63 days**			**Regimen, home miso**	**Total: 92.9%**	**Serious AEs r 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 a Vomiting 22% Fever/chills 3**
						GA	***800 mcg dose:*** ***≤ 42: 95.8%*** ***43-49: 96.2%*** ***50-56: 98.5%*** ***57-63: 93.0%***	
						2nd dose of miso	***2nd 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**

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 findi
								Hemorrhage 0
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	2nd 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 2nd miso dose)	Higher rates o nausea, diarrh warmth/chills immediate mi SAEs: transfu 0.4% (all in 24 group); acute infx, treated a 0.9% (equally each group)
		With 24-hr interval by GA:				*GA*	*24-hr interval; only a single miso dose:*	

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 findi
		≤ 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 hospitalizati 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 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* 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	Hospitalizatio 0.3% Transfusion:

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 findi
							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	2nd 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: Hospitalizatio 0.6% Sepsis 0.2% Common AEs reported
						2nd 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 1st dose		*Regimen,* 2nd dose of miso	2nd dose: 80% success (N=5)	
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		2nd dose miso	2nd dose: 91-100% success	Infection 0.01 Transfusions 0.6% Hospitalizatio 0.9% Buccal vs. ora ↓nausea, ↑dia fever, dizzines
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%*	2nd dose of mi bleeding or

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 findi
Ukraine, Rep. of Georgia, India, Tunisia	OL	days, 325 at 64-70 days)				2nd 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 blee 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	2nd dose of miso part of regimen	2nd 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 3
						GA	*800 mcg dose:* *≤ 42: 95.8%* *43-49: 96.2%* *50-56: 98.5%* *57-63: 93.0%*	
						2nd dose of miso	2nd dose (all GA, both miso dose arms):	

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 findi
							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	2nd dose miso	2nd dose: 62% success N=68	
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
		Buccal by GA: ≤ 49: 226 50-63: 38				*GA*	Buccal: *≤ 49: 96.6%* *50-63: 100%*	
						2nd 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	2nd 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								

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 findi
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2nd 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: (Hospitalizatio 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 1st 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 g hosp for bleed underwent SA No transfusio Hospitalizatio
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 r 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% Hospitalizatio 0.9%
						Dose interval	*24 hr: 94.2%* *24-48 hr: 96.8%*	Buccal vs. ora ↓nausea, ↑dia

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 findi
						2nd dose miso	*91-100% success*	fever, dizzines
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%	2nd dose of mi bleeding or incomplete MA 57-63: 5.7% 64-70: 10.5% Surgery for excessive/pro bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for blee 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 m frequent with

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 findi
		426 oral)					*arm*	
Blum, Raghavan et al. 2012 Tunesia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			*Regimen, home miso*	*Total: 92.9%*	Serious AEs r 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*	*Total: 96.4% (Either dose)*	↑ AEs in 800 a Vomiting 22% Fever/chills 3
						GA	≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%	
						2nd 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%	

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 findi
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)	63 days	2nd 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 2nd miso dose)*	Higher rates o nausea, diarrh warmth/chills immediate mis SAEs: transfu 0.4% (all in 24 group); acute infx, treated a 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 2nd miso dose)*	Side effects d the interval b/ and miso were higher in the 2 hr group; rate nausea & vom after miso dos were also sig. in the 23-25 hr group. Transfusion 0 (equal across
		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%	

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 findi
								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 c 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 hospitaliza Common AEs reported
		Buccal by GA: ≤ 49: 226 50-63: 38				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:

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 findi
								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 Hospitalizatio 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*	Hospitalizatio 0.3% Transfusion:
						Time of f/u	Logistic regression – no difference in	

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 findi
							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% (mai 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 undete hCG: 0.7%; LTFU NS diffe
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%

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 findi
								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 1st dose	Oral miso	Follow-up (sono vs. hCG) *2nd dose of miso*	Total: 98.2% *N=28 Success rate not provided*	2 aspirations hemorrhage
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, 2nd 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 transfusio Hospitalizatio
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

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 findi
							36-42: 98..8% *43-49: 98.1%* *50-56: 96.9%* *57-63: 95.5%*	Infx req'g hospitalizatio 0.01% Total hospital 0.04% Transfusion 0
		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	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%	
Phelps 2001 US	Prospective	28 (Age 14-17)	56 days		Vaginal miso	Adolescents	100%	Common AEs effects") repo "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 complic 0.31%

(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	2nd 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
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1st 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, *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 (≤ 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		
						2nd 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%); 2nd 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 Tunesia & 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%*		
						2nd 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, *follow-up***	**Phone arm: 94.8%** **Clinic arm: 94.6%**		**Ngoc 2014 Vietnam**
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	**OL**	**1,000**	**63 days**	**2nd 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		*GA*	*≤49: 98.0%* *50-56: 96.8%* *57-63: 95.9%*	reported	single miso dose
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 2nd 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)*		
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 2nd 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*	*24-hr interval (1 or more miso doses):* *≤ 49: 98.4%* *50-56: 97.5%* *57-63: 98.3%*		

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
								group)	
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) *GA*	Buccal: 97.1% *Buccal:* *≤ 49: 96.6%* *50-63: 100%*	No hospitalizations Common AEs reported	
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) *Proposed regimen by GA*	*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	2nd 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%); 2nd 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 Tunesia & 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%*		
						2nd dose of miso	*2nd 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**	**2nd 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 2nd 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 Mife
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		*Regimen* 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	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

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	2nd 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
						2nd 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 1st dose		*Regimen,* 2nd dose of miso	2nd dose: 80% success (N=5)		
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		2nd dose miso	2nd 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%*	2nd 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)				2nd dose of miso	2nd 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	2nd dose of miso part of regimen	2nd 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%*		
						2nd dose of miso	2nd 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	2nd dose miso	2nd dose: 62% success N=68		Creinin 2004 Creinin 2007 Did not evaluate 2nd dose in orig papers
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	
		Buccal by GA: ≤ 49: 226 50-63: 38				*GA*	Buccal: *≤ 49: 96.6%* *50-63: 100%*		
						2nd 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	2nd 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	2nd 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 1st 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%*		
						2nd 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%	2nd 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 Tunesia & 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%		
						2nd 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	2nd 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	*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 2nd 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)		
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 2nd 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 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	
		Buccal by GA: ≤ 49: 226 50-63: 38				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 1st dose	Oral miso	Follow-up (sono vs. hCG) *2nd 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, 2nd 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%	
		By age: < 18: 605 18-24: 6,684 25-29: 3,317				Data on 322 females age 11-16 years and 283 age 17 years	Success by age: < 18: 98.7% 18-24: 98.1% 25-29: 97.5%		Applicant obtained GA-stratified

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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04/06/2016

This table was inadvertently truncated when appended to my original CDTL review and is included here for completeness.

Exhibit 1C

(Slip Opinion)

Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions

Section 1461 of title 18 of the U.S. Code does not prohibit the mailing of certain drugs that can be used to perform abortions where the sender lacks the intent that the recipient of the drugs will use them unlawfully. Because there are manifold ways in which recipients in every state may lawfully use such drugs, including to produce an abortion, the mere mailing of such drugs to a particular jurisdiction is an insufficient basis for concluding that the sender intends them to be used unlawfully.

December 23, 2022

MEMORANDUM OPINION FOR THE GENERAL COUNSEL
UNITED STATES POSTAL SERVICE

In the wake of the United States Supreme Court's recent decision overruling *Roe v. Wade*, 410 U.S. 113 (1973),[1] you have asked for this Office's view on whether section 1461 of title 18 of the United States Code prohibits the mailing of mifepristone and misoprostol, two prescription drugs that are commonly used to produce abortions,[2] among other purposes. Memorandum for Christopher Schroeder, Assistant Attorney General, Office of Legal Counsel, from Thomas J. Marshall, General Counsel, United States Postal Service, *Re: Request for an Interpretation of 18 U.S.C. § 1461*, at 1 (July 1, 2022) ("USPS Request"). Originally enacted as part of the Comstock Act of 1873, section 1461 currently declares "[e]very article or thing designed, adapted, or intended for producing abortion," as well as "[e]very article, instrument, substance, drug, medicine, or thing which is advertised or described in a manner calculated to lead another to use or apply it for producing abortion," to be "nonmailable matter" that the United States Postal Service ("USPS") may not lawfully deliver. 18 U.S.C. § 1461.

We conclude that section 1461 does not prohibit the mailing, or the delivery or receipt by mail, of mifepristone or misoprostol where the sender

[1] *See Dobbs v. Jackson Women's Health Org.*, 142 S. Ct. 2228 (2022).

[2] *See* Ctrs. for Disease Control & Prevention, U.S. Dep't of Health & Hum. Servs., *Abortion Surveillance—United States, 2019*, 70 MMWR Surveillance Summaries, Nov. 26, 2019, at 8, https://www.cdc.gov/mmwr/volumes/70/ss/ss7009a1.htm.

lacks the intent that the recipient of the drugs will use them unlawfully.[3] This conclusion is based upon a longstanding judicial construction of the Comstock Act, which Congress ratified and USPS itself accepted. Federal law does not prohibit the use of mifepristone and misoprostol. Indeed, the U.S. Food and Drug Administration ("FDA") has determined the use of mifepristone in a regimen with misoprostol to be safe and effective for the medical termination of early pregnancy.[4] Moreover, there are manifold ways in which recipients in every state may use these drugs, including to produce an abortion, without violating state law. Therefore, the mere mailing of such drugs to a particular jurisdiction is an insufficient basis for concluding that the sender intends them to be used unlawfully.[5]

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[3] A cognate provision, 18 U.S.C. § 1462, imposes similar abortion-related prohibitions on using an express company or other common carrier for "carriage" of such items. Our analysis in this memorandum is applicable to that provision as well.

Sections 1461 and 1462 refer not only to persons who transmit such items by mail or by common carrier—the senders—but also to individuals who "knowingly cause[]" such items to be mailed, *id.* § 1461; "knowingly take[]" any such items from the mail for the purpose of circulating or disposing of them, *id.*; or "knowingly take[] or receive[]" such items from an express company or common carrier, *id.* § 1462. In the different contexts of obscenity and child pornography, courts of appeals have held that section 1461 applies to the act of the recipient who orders the nonmailable material and thereby "causes" it to be mailed. *See, e.g.*, *United States v. Carmack*, 910 F.2d 748, 748 (11th Cir. 1990); *United States v. Johnson*, 855 F.2d 299, 305–06 (6th Cir. 1988). *But see Johnson*, 855 F.2d at 307–11 (Merritt, J., dissenting); *United States v. Sidelko*, 248 F. Supp. 813, 815 (M.D. Pa. 1965). As far as we know, however, these provisions have never been applied to prosecute the recipients of abortion- and contraception-related materials. Moreover, the court of appeals decisions we discuss below construed the relevant provisions of the Comstock Act to turn on the nature of the sender's intent, not that of the recipient. Consistent with this practice, we focus on the sender throughout this memorandum. To the extent a recipient might be covered, however, our analysis herein would apply and therefore section 1461 would not prohibit that person from ordering or receiving the drugs if she does not intend that they be used unlawfully.

[4] *See Mifeprex (Mifepristone) Tablets*, U.S. Food & Drug Admin. 2 (Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf (mifepristone label); *see also Mifeprex (Mifepristone) Information*, U.S. Food & Drug Admin., https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/mifeprex-mifepristone-information (last updated Dec. 16, 2021).

[5] For purposes of this opinion, we assume but do not decide that section 1461 could be constitutionally applied to the mailing of drugs intended to produce abortions. We also assume without deciding that state law, as well as federal, is relevant to the application of section 1461. In addition, we do not address here whether and under what circumstances the mailing of mifepristone or misoprostol might violate other federal laws. Finally, as

I.

The Comstock Act has a long and complex history. The original 1873 law was the handiwork of Anthony Comstock—"a prominent anti-vice crusader who believed that anything remotely touching upon sex was . . . obscene"—who successfully lobbied Congress and state legislatures in the nineteenth century to enact expansive laws "to prevent the mails from being used to corrupt the public morals." *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 70 n.19 (1983) (omission in original) (quotation marks and citations omitted); *see also* Priscilla J. Smith, *Contraceptive Comstockery: Reasoning from Immorality to Illness in the Twenty-First Century*, 47 Conn. L. Rev. 971, 982–84 (2015). Originally entitled "An Act for the Suppression of Trade in, and Circulation of, obscene Literature and Articles of immoral Use," Act of Mar. 3, 1873, ch. 258, 17 Stat. 598 ("1873 Act"), the Act is perhaps best known for having prohibited the distribution of a wide range of writings until courts and the Executive Branch determined that the Free Speech Clause of the First Amendment significantly limited the permissible reach of the law, *see, e.g.*, *Bolger*, 463 U.S. at 69–75. In addition, the Act also included several restrictions on the conveyance of things designed to prevent conception or to produce abortion.[6] Congress largely repealed the references to contraceptives in

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you note, USPS Request at 3, some states have independently enacted laws to restrict the mailing of these drugs for abortion purposes within their jurisdiction. *See, e.g.*, Tex. Health & Safety Code § 171.063(b-1). We do not here assess the possible effect of federal law on such state restrictions, other than to note our agreement with your view that the doctrine of intergovernmental immunity would preclude application of such state laws against USPS employees who are complying with their duties under federal law. *See Intergovernmental Immunity for the Department of Veterans Affairs and Its Employees When Providing Certain Abortion Services*, 46 Op. O.L.C. __, at *1–5, *10 (Sept. 21, 2022).

[6] The original 1873 Act consisted of five sections, three of which are relevant to this opinion. Section 1 of the Act prohibited, *inter alia*, the sale, distribution, or possession, in the District of Columbia and federal territories, of "any drug or medicine, or any article whatever, for the prevention of conception, or for causing *unlawful* abortion," along with advertisements for contraceptives and abortion services and information about how to obtain them. 1873 Act § 1, 17 Stat. at 598–99 (emphasis added). Congress chose not to include that prohibition when it comprehensively enacted title 18 into positive law in 1948. *See* Pub. L. No. 80-772, § 21, 62 Stat. 683, 864 (1948) (repealing, *inter alia*, 18 U.S.C. § 512 (1946)).

Section 2 of the Act, which eventually became codified as section 1461, criminalized the mailing of, *inter alia*, "obscene, lewd, or lascivious" writings; "any article or thing

1971. *See* Pub. L. No. 91-662, 84 Stat. 1973 (1971) (discussed *infra* Part I.C).

In its current form, section 1461, which is derived from section 2 of the 1873 Act, begins by declaring "[e]very obscene, lewd, lascivious, indecent, filthy or vile article, matter, thing, device, or substance" to be "nonmailable matter" that "shall not be conveyed in the mails or delivered from any post office or by any letter carrier." 18 U.S.C. § 1461. The next clauses declare nonmailable "[e]very article or thing designed, adapted, or intended for producing abortion, or for any indecent or immoral use; and [e]very article, instrument, substance, drug, medicine, or thing which is advertised or described in a manner calculated to lead another to use or apply it for producing abortion, or for any indecent or immoral purpose." *Id.*; *see also* 39 U.S.C. § 3001(a) (likewise declaring such matter to be "nonmailable"). Section 1461 further makes it a felony to "knowingly use[] the mails for the mailing, carriage in the mails, or delivery" of any such things, or to "knowingly cause[]" them "to be delivered by mail according to the direction thereon." 18 U.S.C. § 1461. In addition, 18 U.S.C. § 1462 imposes two other, related prohibitions: it makes it unlawful to bring those same things "into the United States, or any place subject to the jurisdiction thereof," and it prohibits the knowing use of "any

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intended or adapted for any indecent or immoral use or nature"; and "any article or thing designed or intended for the prevention of conception or procuring of abortion." 1873 Act § 2, 17 Stat. at 599. Before Congress enacted title 18 into positive law in 1948, the provision that is now section 1461 was codified at 18 U.S.C. § 334 (1925–1926).

Section 3 of the 1873 Act prohibited all persons "from importing into the United States" any of the "hereinbefore-mentioned articles or things"—referring to the items prohibited by sections 1 and 2. 1873 Act § 3, 17 Stat. at 599. One year later, *see* Act of June 20, 1874, ch. 333, 18 Stat. pt. 3, at 113–14, Congress codified section 3 of the Comstock Act as section 2491 of the Revised Statutes and, in doing so, replaced the section's reference to the "hereinbefore-mentioned articles or things" with a list of articles and things pulled from the other provisions of the Comstock Act, *see* Rev. Stat. § 2491 (1st ed. 1875), 18 Stat. pt. 1, at 460; *see also* Rev. Stat. § 2491 (2d ed. 1878), 18 Stat. pt. 1, at 457. In supplying content to these words, Congress prohibited the importation of articles or things "for causing unlawful abortion," reflecting the language of section 1 of the original Comstock Act. Rev. Stat. § 2491 (1st ed. 1875), 18 Stat. pt. 1, at 460. Congress consistently retained the words "unlawful abortion" in follow-on versions of this restriction, including in subsequent Tariff Acts through 1930, after which the provision was codified at 19 U.S.C. § 1305.

express company or other common carrier or interactive computer service" for "carriage" of such items "in interstate or foreign commerce."[7]

Over the course of the last century, the Judiciary, Congress, and USPS have all settled upon an understanding of the reach of section 1461 and the related provisions of the Comstock Act that is narrower than a literal reading might suggest. This construction occurred long before the Supreme Court's decisions in *Griswold v. Connecticut*, 381 U.S. 479 (1965), and *Roe* and thus was not dependent upon the Court's recognition of constitutional rights regarding the prevention or termination of pregnancy. Beginning early in the twentieth century, federal courts construed the provisions not to prohibit all mailing or other conveyance of items that can be used to prevent or terminate pregnancy. By the middle of the century, the well-established, consensus interpretation was that none of the Comstock Act provisions, including section 1461, prohibits a sender from conveying such items where the sender does not intend that they be used unlawfully. USPS accepted that construction and informed Congress of it. On several occasions, Congress reenacted and amended the Comstock Act against the backdrop of the judicial precedent in a manner that ratified the federal courts' narrowing construction.

A.

Since early in the twentieth century, federal courts have agreed that section 1461 and related Comstock Act provisions do not categorically prohibit the mailing or other conveyance of items designed, adapted, or intended for preventing or terminating pregnancy.

In 1915, in *Bours v. United States*, 229 F. 960 (7th Cir. 1915), the U.S. Court of Appeals for the Seventh Circuit reversed the conviction of a doctor who had mailed a letter addressing how a woman might procure an "operation" from him. The court noted that Congress enacted the provision that is now section 1461 pursuant to its "national power of controlling the mails" and held that, "[i]n applying the national statute to an alleged offensive use of the mails at a named place, it is immaterial what

[7] The importation prohibition—along with 19 U.S.C. § 1305 (prohibiting the importation into the United States of "any drug or medicine or any article whatever for causing unlawful abortion")—derives from section 3 of the original 1873 Act, *see* § 3, 17 Stat. at 599. The common-carrier prohibitions derive from an 1897 law extending the mailing prohibitions of the original Comstock Act to common carriers. *See* Act of Feb. 8, 1897, ch. 172, 29 Stat. 512.

the local statutory definition of abortion is, what acts of abortion are included, or what excluded." *Id.* at 964. The court further held that "[t]hough the letter of the statute would cover all acts of abortion," under a "reasonable construction," the statute should not be read to prohibit the mailing of advertisements for a procedure a doctor would perform in order "to save [the] life" of the woman. *Id.* Because the indictment had not drawn this distinction, the defendant had no opportunity to explain whether he had intended to perform the operation "only under such circumstances as would make it the duty of any reputable physician to perform the act." *Id.* at 965. Therefore, the court reversed the judgment and remanded the case. *Id.* at 966.

Fifteen years later, in *Youngs Rubber Corp. v. C.I. Lee & Co.*, 45 F.2d 103 (2d Cir. 1930), the U.S. Court of Appeals for the Second Circuit also reasoned in dicta that the statute could not be construed as expansively as its language might suggest. *Youngs Rubber* was a trademark infringement suit in which the defendants argued that the plaintiff's business was unlawful because it involved sending Trojan condoms to druggists for retail sale via the mail and common carriage, a practice that—according to the defendant—violated the Comstock Act. *Id.* at 108. "Taken literally," the appeals court wrote, the Comstock Act's "language would seem to forbid the transportation by mail or common carriage of anything 'adapted,' in the sense of being suitable or fitted, for preventing conception or for any indecent or immoral purpose, even though the article might also be capable of legitimate uses and the sender in good faith supposed that it would be used only legitimately." *Id.* "Such a construction," the court cautioned, "would prevent mailing to or by a physician of any drug or mechanical device 'adapted' for contraceptive or abortifacient uses, although the physician desired to use or to prescribe it for proper medical purposes." *Id.* The court observed that New York law did not prohibit supplying such articles to physicians "or by their direction or prescription." *Id.* at 109 (quotation marks omitted). Reasoning that "[t]he intention to prevent a proper medical use of drugs or other articles merely because they are capable of illegal uses is not lightly to be ascribed to Congress," the court construed the statute's contraception and abortion prohibitions to "requir[e] an intent on the part of the sender that the article mailed or shipped by common carrier be used for illegal contraception or abortion." *Id.* at 108.

In 1933, the U.S. Court of Appeals for the Sixth Circuit embraced the same limiting construction of the Comstock Act. *Davis v. United States*,

62 F.2d 473 (6th Cir. 1933), involved a defendant who was convicted of, among other things, the sale of "rubber sundries" to druggists that were delivered by common carrier. *Id.* at 474. Invoking the "rule of reasonable construction," *id*. at 475, the *Davis* court reversed the conviction because the district court did not permit the admission of evidence that the defendant had sent the items intending that they be used for "treatment and prevention of disease" rather than to prevent conception, *id.* at 474. The court quoted with approval *Youngs Rubber*'s view that the statute should be read to "requir[e] an intent on the part of the sender that the article mailed or shipped by common carrier be used for illegal contraception or abortion or for indecent or immoral purposes," *id.*, and noted that the "soundness of its reasoning commends itself to us," *id.* at 475. The court accordingly rejected the district court's conclusion that the statute "brings within the condemnation of each section articles or things that are capable of being used for the specified purposes without respect to their having a legitimate use, and without regard to the intent of the persons mailing [them]," *id.* at 474, holding instead that "intent that the articles . . . shipped in interstate commerce were to be used for condemned purposes is a prerequisite to conviction," *id.* at 475.

Three years later, the Second Circuit revisited the issue and adopted *Youngs Rubber*'s dicta as a holding in *United States v. One Package*, 86 F.2d 737 (2d Cir. 1936). In that case, a New York gynecologist had imported vaginal pessaries from a Japanese sender who had asked the doctor to use them in her practice to assess whether they were useful for contraceptive purposes. *Id.* at 738. At the time, New York law prohibited the sale or provision of articles for the prevention of conception, but it included an exception for the provision of such things to physicians "who may in good faith prescribe their use for the cure or prevention of disease." *Id.* (citing N.Y. Penal Law § 1145 (Consol. Laws, c. 40)). The doctor testified that she prescribed the items only where her patient had a health-related reason such that "it would not be desirable for a patient to undertake a pregnancy," which the court of appeals apparently understood to fall within the exception under New York law that permitted physicians to provide patients with contraceptives for particular purposes. *Id.*[8] The court quoted favorably, and at length, from the dicta in *Youngs Rubber*, and noted the accord of the Sixth Circuit in *Davis*. *Id.* at 738–39. It then

[8] The court of appeals noted that the accuracy and good faith of the doctor's testimony was "not questioned." *One Package*, 86 F.2d at 738.

dismissed the case because none of the relevant provisions should be read to prohibit the mailing or importation of items to prevent or terminate pregnancy with the intent that they be used for lawful purposes. *Id.* at 739–40. The court reasoned that it was appropriate to, in effect, imply the insertion of the adjective "unlawful," which expressly modified the word "abortion" in some provisions of the Comstock Act, to modify the terms "prevention of conception" and "abortion" throughout the various provisions that derived from the Act. *Id.* [9] The court elaborated:

> [W]e are satisfied that this statute, as well as all the acts we have referred to, embraced only such articles as Congress would have denounced as immoral if it had understood all the conditions under which they were to be used. Its design, in our opinion, was not to prevent the importation, sale, or carriage by mail of things which might intelligently be employed by conscientious and competent physicians for the purpose of saving life or promoting the well being of their patients. The word "unlawful" would make this clear as to

[9] The case involved the "prevention of conception" prong of the Tariff Act of 1930—a descendent provision of the original Comstock Act—which prohibited importing articles "for the prevention of conception or for causing *unlawful* abortion." *One Package*, 86 F.2d at 738 (emphasis added) (quoting 19 U.S.C. § 1305(a) (1934)); *see also supra* note 6. The court noted that the original 1873 Comstock Act likewise used the adjective "unlawful" to modify "abortion" in one of its provisions (section 1—involving the sale and possession of abortifacients in federal territories) but not in others, and not as to articles for preventing conception. *One Package*, 86 F.2d at 739. The court reasoned that Congress could not reasonably have had the design to make the "unlawful" nature of the intended use an element of the offense under some of the abortion-related prohibitions but not others, or as to the importation of items used for abortion but not those used for contraception. *See id.* ("[I]n the Comstock Act, . . . the word 'unlawful' was sometimes inserted to qualify the word 'abortion,' and sometimes omitted. It seems hard to suppose that under the second and third sections articles intended for use in procuring abortions were prohibited in all cases while, under the first section, they were only prohibited when intended for use in an 'unlawful abortion.'"). Instead, the court reasoned, the adjective "unlawful" must in effect be read to modify all of the prohibitions. *Id.*; *see also id.* at 740 (Learned Hand, J., concurring) ("[I]t is of considerable importance that the law as to importations should be the same as that as to the mails; we ought not impute differences of intention upon slight distinctions in expression."). The *One Package* court's analysis that the adjective "unlawful" should be read to modify all of the provisions of the Comstock Act is bolstered by the 1874 Congress's understanding of the term "hereinbefore-mentioned articles" in section 3 of the Comstock Act to prohibit the import only of articles, drugs, or medicines "for causing unlawful abortion." *See supra* note 6; Rev. Stat. § 2491 (1st ed. 1875), 18 Stat. pt. 1, at 460.

> articles for producing abortion, and the courts have read an exemption into the act covering such articles even where the word "unlawful" is not used. The same exception should apply to articles for preventing conception. . . . It seems unreasonable to suppose that the national scheme of legislation involves such inconsistencies and requires the complete suppression of articles, the use of which in many cases is advocated by such a weight of authority in the medical world.

Id.

The Second Circuit again reaffirmed this construction of the statute shortly thereafter in *United States v. Nicholas*, 97 F.2d 510 (2d Cir. 1938), which involved the Comstock Act's prohibition on mailing information about contraception. Citing *Youngs Rubber* and *One Package*, the court in *Nicholas* noted: "We have twice decided that contraceptive articles may have lawful uses and that statutes prohibiting them should be read as forbidding them only when unlawfully employed." *Id*. at 512.[10] Applying this reading, the court held that USPS was required to deliver a magazine containing contraception-related information to a magazine editor who might then distribute it to persons such as physicians who could use the information lawfully. *Id.* The court further held that USPS should detain a book containing such information when it was addressed to an individual "about whom nothing" was known "except that he was not a physician," *id.* at 511, but allowed for the recipient to "prove whether he is among the privileged classes" whose possession of the book "would be lawful," *id.* at 512.

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[10] Although *Nicholas* described the relevant inquiry as being whether the articles were "unlawfully employed," rather than whether the sender *intended* that they be used unlawfully—the touchstone the court had adopted in *Youngs Rubber* and *One Package*—this difference in phrasing does not reflect a departure relevant to our analysis. The court's invocation of those two earlier decisions without qualification, as well as its further citation to *Davis*, indicates that it did not intend to deviate from the interpretation of the Act that the court had adopted in those decisions. Both the Historical and Revision Note to section 1461 and subsequent federal decisions understood *Nicholas* similarly. *See* 18 U.S.C. § 1461 (Historical and Revision Note) (observing that *Nicholas* followed "[t]he same rule" as *Davis*, which held that "the *intent* of the person" that a mailing "be used for condemned purposes was necessary for a conviction" (emphasis added)); *United States v. Gentile*, 211 F. Supp. 383, 385 n.5 (D. Md. 1962) (citing, *inter alia*, *Nicholas* for the proposition that "contraceptive devices [must be] shipped and received with intent that they be used for *illegal* contraception or abortion").

In 1944, the U.S. Court of Appeals for the D.C. Circuit also narrowly construed the statute in the context of a report about contraceptive materials that a consumer group had published and mailed to individuals who submitted a signed certificate attesting, "I am married and use prophylactic materials on the advice of a physician." *Consumers Union of United States, Inc. v. Walker*, 145 F.2d 33, 33 (D.C. Cir. 1944). The appeals court explained that it was "inclined to follow the interpretation [of the Comstock Act] which has been adopted in other circuits," citing to *Nicholas*, *Davis*, *Youngs Rubber*, and *One Package*. *Id.* at 35 & n.11. It therefore concluded that "Congress did not intend to exclude from the mails properly prepared information intended for properly qualified people," and held that the report "was proper in character within the meaning of those decisions." *Id*. at 35.

Subsequent judicial discussions of the relevant Comstock Act provisions recognized the narrowing construction upon which the courts of appeals had converged. *See, e.g.*, *United States v. Gentile*, 211 F. Supp. 383, 385 n.5 (D. Md. 1962) ("It seems clear under the authorities that in order to make out an offense under this paragraph the Government should be required to allege and prove that contraceptive devices are shipped and received with intent that they be used for *illegal* contraception or abortion or for indecent or immoral purposes." (citing *Youngs Rubber*, *Davis*, and *Nicholas*)); *United States v. H.L. Blake Co.*, 189 F. Supp. 930, 934–35 (W.D. Ark. 1960) ("It would seem reasonable to give the word 'adapted' a more limited meaning than that above suggested and to construe the whole phrase 'designed, adapted or intended' as requiring an intent on the part of the sender that the article mailed or shipped by common carrier be used for illegal contraception or abortion or for indecent or immoral purposes." (quoting *Youngs Rubber*, 45 F.2d at 108)); *United States v. 31 Photographs*, 156 F. Supp. 350, 357 (S.D.N.Y. 1957) (characterizing the appellate court decisions as "upholding importation of contraceptives and books dealing with contraception when sought to be brought into the country for purposes of scientific and medical research," such that "only contraceptives intended for 'unlawful' use were banned" (citing, *inter alia*, *One Package*, *Nicholas*, *Davis*, and *Walker*)); *see also Poe v. Ullman*, 367 U.S. 497, 546 n.12 (1961) (Harlan, J., dissenting) ("[B]y judicial interpretation . . . the absolute prohibitions of the [Comstock] law were qualified to exclude professional medical use." (citing *Youngs Rubber*, *Davis*, and *One Package*)).

As the court in one of those later cases noted, the analysis in *Youngs Rubber* "has been cited many times and has become the law to be applied to the facts where the question of a violation of the statute . . . is before the court." *H.L. Blake Co.*, 189 F. Supp. at 934. Under that "law to be applied," the court explained, "it is well established that the defendants should not be convicted unless it is established beyond a reasonable doubt that at the time they mailed the sample packages of prophylactics . . . they intended them to 'be used for illegal contraception.'" *Id.* at 935 (quoting *Youngs Rubber*, 45 F.2d at 108).[11]

B.

Congress has amended the Comstock Act's provisions numerous times since the federal courts' decisions in *Bours*, *Youngs Rubber*, *Davis*, *One Package*, *Nicholas*, and *Walker*, each time perpetuating the wording of the Act's abortion-related provisions. Moreover, as we explain in greater detail below, USPS accepted the courts' narrowing construction of the Act in administrative rulings, and it informed Congress of the agency's acceptance of that construction in connection with Congress's amendment of the contraception-related provisions of the Comstock Act.

We conclude that Congress's repeated actions, taken "[a]gainst this background understanding in the legal and regulatory system," *Texas Dep't of Housing & Cmty. Affs. v. Inclusive Cmtys. Project*, 576 U.S. 519, 536 (2015), ratified the Judiciary's settled narrowing construction. *See id.* ("If a word or phrase has been . . . given a uniform interpretation by inferior courts . . . , a later version of that act perpetuating the wording is presumed to carry forward that interpretation." (omissions in original) (quoting Antonin Scalia & Bryan A. Garner, Reading Law: The Interpre-

[11] The leading cases that established this accepted construction—*Youngs Rubber*, *One Package*, and *Davis*—each involved items that could be used to prevent conception rather than to produce abortion. Nevertheless, the canonical passage from *Youngs Rubber*, repeated in each of the cases and in others thereafter, referred both to items designed to prevent conception and to those designed to induce abortions. Moreover, the court in *One Package* went to lengths to explain that all of the relevant Comstock Act prohibitions should be read consistently to require proof of a sender's intent to facilitate unlawful downstream use. *See supra* note 9; *see also Bours*, 229 F. 960 (construing narrowly the prohibition on mailing of information about how to obtain abortions). We therefore agree with your assessment that "there is no apparent reason why the case-law principles applicable to contraceptive articles (formerly) under Section 1461 would not also apply to abortion-inducing articles under the same provision." USPS Request at 3 n.3.

tation of Legal Texts 322 (2012))); *Lorillard v. Pons*, 434 U.S. 575, 580 (1978) ("Congress is presumed to be aware of an administrative or judicial interpretation of a statute and to adopt that interpretation when it reenacts a statute without change."); *cf. Bragdon v. Abbott*, 524 U.S. 624, 645 (1998) ("When administrative and judicial interpretations have settled the meaning of an existing statutory provision, repetition of the same language in a new statute indicates, as a general matter, the intent to incorporate its administrative and judicial interpretations as well."); *Forest Grove Sch. Dist. v. T.A.*, 557 U.S. 230, 244 n.11 (2009) (holding that when Congress amended the Individuals with Disabilities Education Act without altering the text of a provision that the Supreme Court had previously interpreted, Congress "implicitly adopted [the Court's] construction of the statute").

The conclusion that Congress ratified the longstanding judicial view of the Comstock Act is strongly reinforced by the Historical and Revision Note that was included in the 1945 report of the House Committee on the Revision of the Laws[12] when Congress enacted title 18 of the U.S. Code into positive law.[13] That Note subsequently was appended to the official U.S. Code entries for sections 1461 and 1462. *See* 18 U.S.C. § 1461 (Historical and Revision Note).[14] It specifically "invited" the "attention of Congress" to the courts of appeals' decisions in *Youngs Rubber*, *Davis*, *Nicholas*, and *One Package*, and quoted at length from *Youngs Rubber*, including its conclusion that the relevant provisions of the statute should be construed to require "an intent on the part of the sender that the article

[12] *See* H.R. Rep. No. 79-152, at A96–97 (1945).

[13] *See* Pub. L. No. 80-772, 62 Stat. at 768.

[14] The Historical and Revision Notes were written by a staff of experts hired by Congress to revise the U.S. Code in the 1940s, including the editorial staffs of the West and Thompson publishing companies, the former Chief of the Appellate Section of the Department of Justice Criminal Division, and other contributors from both inside and outside of government. *See* H.R. Rep. No. 79-152, at 1–7 (1945) (describing in detail this revision process and noting that "[t]he [House] Committee on Revision of the Laws has exercised close and constant supervision over this work through its general counsel . . . and its special counsel"). The Supreme Court has discussed or relied on Historical and Revision Notes numerous times, most frequently during the middle of the twentieth century. *See, e.g.*, *Ex parte Collett*, 337 U.S. 55, 65–71 (1949) (discussing a revision note to 28 U.S.C. § 1404 and concluding that the revision note was highly significant in determining the meaning of section 1404(a)); *W. Pac. R.R. Corp. v. W. Pac. R.R. Co.*, 345 U.S. 247, 254–55 (1953); *Muniz v. Hoffman*, 422 U.S. 454, 471–73 (1975).

mailed or shipped by common carrier be used for illegal contraception or abortion." *Id.*[15]

Congress subsequently amended the Comstock Act four times (in 1955, 1958, 1971, and 1994) without changing the language in any respect that suggested disagreement with the well-established narrowing interpretation that the Historical and Revision Note had specifically brought to its attention. Congress made the third of these amendments in 1971—removing the Act's references to contraceptives—after being informed by the Post-

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[15] The Note's complete discussion of the court of appeals decisions is as follows:

> The attention of Congress is invited to the following decisions of the Federal courts construing this section and section 1462 of this title.
>
> In *Youngs Rubber Corporation, Inc. v. C. I. Lee & Co., Inc.*, C.C.A. 1930, 45 F. 2d 103, it was said that the word "adapted" as used in this section and in section 1462 of this title, the latter relating to importation and transportation of obscene matter, is not to be construed literally, the more reasonable interpretation being to construe the whole phrase "designed, adapted or intended" as requiring "an intent on the part of the sender that the article mailed or shipped by common carrier be used for illegal contraception or abortion or for indecent or immoral purposes." The court pointed out that, taken literally, the language of these sections would seem to forbid the transportation by mail or common carrier of anything "adapted," in the sense of being suitable or fitted, for preventing conception or for any indecent or immoral purpose, "even though the article might also be capable of legitimate uses and the sender in good faith supposed that it would be used only legitimately. Such a construction would prevent mailing to or by a physician of any drug or mechanical device 'adapted' for contraceptive or abortifacient uses, although the physician desired to use or to prescribe it for proper medical purposes. The intention to prevent a proper medical use of drugs or other articles merely because they are capable of illegal uses is not lightly to be ascribed to Congress. Section 334 [this section] forbids also the mailing of obscene books and writings; yet it has never been thought to bar from the mails medical writings sent to or by physicians for proper purposes, though of a character which would render them highly indecent if sent broadcast to all classes of persons." In *United States v. Nicholas*, C.C.A. 1938, 97 F. 2d 510, ruling directly on this point, it was held that the importation or sending through the mails of contraceptive articles or publications is not forbidden absolutely, but only when such articles or publications are unlawfully employed. The same rule was followed in *Davis v. United States*, C.C.A. 1933, 62 F. 2d 473, quoting the obiter opinion from *Youngs Rubber Corporation v. C. I. Lee & Co.*, *supra*, and holding that the intent of the person mailing a circular conveying information for preventing conception that the article described therein should be used for condemned purposes was necessary for a conviction; also that this section must be given a reasonable construction. (See also *United States v. One Package*, C.C.A. 1936, 86 F. 2d 737.)
>
> 18 U.S.C. § 1461 (Historical and Revision Note).

master General that both the federal courts and USPS had adopted this narrowing interpretation. *See* H.R. Rep. No. 91-1105, at 3–4 (1970).[16] Moreover, we have found no evidence that Congress disapproved of the interpretation.[17] Indeed, in 2007 Congress legislated regarding the FDA's treatment of mifepristone in a manner consistent with the understanding that the Comstock Act does not categorically prohibit the covered modes of conveying abortion-inducing drugs.[18]

Congress's several actions "perpetuating the wording" of the Comstock Act's abortion provisions against the backdrop of a well-established, settled judicial construction that was brought to Congress's attention

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[16] *See supra* note 11 (explaining that the courts of appeals' rationales applied equally to conveyance of items to prevent conception and to produce abortion).

[17] The House report stated at the outset of its discussion that "[e]xisting statutes completely prohibit the importation, interstate transportation, and mailing of contraceptive materials, or the mailing of advertisement or information concerning how or where such contraceptives may be obtained or how conception may be prevented." H.R. Rep. No. 91-1105, at 2. That introductory remark, however, plainly was a reference to the literal text of the provisions, as opposed to their settled meaning. The report proceeded to convey the Postmaster General's description of the settled judicial and administrative narrowing construction of the statute, noting that it was in tension with the text of the contraception provisions, and neither the report nor any evidence in the legislative record of which we are aware expresses the committee's disagreement with that construction.

[18] In approving a mifepristone product for certain abortions in 2000, the FDA imposed certain restrictions on distribution as a condition of approval, pursuant to its regulatory authority. *See* Letter for Sandra P. Arnold, Vice President, Population Council, from Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., *Re: NDA 20-687* (Sept. 28, 2000). In the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Congress provided that any such restrictions, identified in the FDAAA as "elements to assure safe use," were deemed to be a "Risk Evaluation and Mitigation Strategy" that would continue to be required under the new statutory regime unless and until the FDA determined that modifications were necessary. *See* Pub. L. No. 110-85, tit. IX, § 909(b), 121 Stat. 823, 950–51 (2007). In the debate preceding this amendment, critics of the FDA's 2000 approval of mifepristone for abortion purposes acknowledged that the legislation would apply to that mifepristone approval. *See* 153 Cong. Rec. S5765 (daily ed. May 9, 2007) (statement of Sen. Coburn); 153 Cong. Rec. S5469–70 (daily ed. May 2, 2007) (statement of Sen. DeMint). Yet neither those critics nor anyone else in the congressional debate mentioned the Comstock Act, even though it would have been natural to assume that the FDA's 2000 approval had resulted in the distribution of mifepristone to certified physicians through the mail or by common carrier. Congress's decision to carry forward the FDA's regulatory conditions for mifepristone without addressing such modes of distribution suggests that Congress did not understand the Comstock Act to invariably prohibit the conveyance by mail or common carrier of drugs intended to induce abortions.

establishes Congress's acceptance of that narrowing construction. *Inclusive Cmtys. Project*, 576 U.S. at 536. That construction, as noted, does not prohibit the mailing of an item that is designed, adapted, or intended for producing abortion in the absence of an intent by the sender that the item will be used unlawfully.

C.

USPS has accepted the settled judicial construction of the Comstock Act—and reported as much to Congress.

In 1951, the Solicitor of the Post Office Department, Roy C. Frank, wrote to an Arizona postmaster concerning a Planned Parenthood clinic's mailing of diaphragms and vaginal jellies to its patients "for medicinal purposes." *Contraceptive Matter—Mailings—Physicians*, 9 Op. Sol. P.O.D. 47 (1951) (No. 40). Citing "the decisions of the Federal courts," Frank opined that a "mailing of contraceptives by a physician to a patient would not be regarded as a violation" of the Comstock Act. *Id.* Similarly, in 1963, when the St. Louis Postmaster detained 490 "contraceptive devices and substances," the USPS General Counsel informed him that he should "dispatch" those items because "there is no available evidence that the items in each of these parcels were being distributed for unlawful purposes." Letter for Harriet F. Pilpel, Greenbaum, Wolff & Ernst, from Louis J. Doyle, General Counsel, Post Office Department (Oct. 24, 1963) (on file with the Smith College Libraries). In a letter to the sender Emko Company's counsel, the USPS General Counsel added that "should we obtain evidence in the future that [Emko] is distributing contraceptive devices and substances for unlawful purposes we will again look into the matter." *Id.*

Of particular importance, when Congress was considering amendments to the Comstock Act in 1970, USPS brought to Congress's attention its acceptance of the Judiciary's narrowing construction. The Postmaster General submitted a statement to Congress about his agency's understanding that "the delivery by mail of contraceptive information or materials has by court decisions, and administrative rulings based on such decisions, been considered proper in cases where a lawful and permissive purpose is present." *See* H.R. Rep. No. 91-1105, at 3–4 (1970). As a result, "[t]he lawful mailing . . . of contraceptive articles . . . is dependent on the interpretation given to the intended purpose." *Id.* at 4. The Postmaster General noted that "[w]hat is a lawful purpose within the meaning

of the interpretations given, though vaguely identifiable, has with the passage of time also been considerably broadened" and that "many States . . . have adopted positive legislation to authorize or encourage public family planning services." *Id.* As a result, by the time the Postmaster General wrote to Congress in 1970—after the Court's *Griswold* decision holding unconstitutional a state prohibition on the use of contraception—"it [was] quite clear that the cited law as presently written [was] unenforceable." *Id.*

The House Ways and Means Committee included the Postmaster General's statement in its report on the draft amendment and noted that "[i]n view of" that statement—along with statements supporting the draft amendment by the Departments of Labor and of Health, Education, and Welfare—the Committee on Ways and Means was "unanimous in recommending enactment of H.R. 4605." *Id.* Congress then amended the Comstock Act to repeal most of the Act's applications to contraceptives. *See* Pub. L. No. 91-662, 84 Stat. at 1973–74.[19]

* * * * *

Thus, before the Court's recognition of a constitutional right to contraception in *Griswold* and to abortion in *Roe*, the Judiciary, Congress, and USPS itself all understood section 1461 and the related provisions of the Comstock Act not to prohibit the conveyance of articles intended for preventing conception or producing an abortion where the sender lacks the intent that those items should be used unlawfully. We further note that, shortly after Congress amended the Comstock Act in 1971 to eliminate the restrictions on contraceptives, the Supreme Court's decision in *Roe* effectively rendered unenforceable the restrictions on articles "designed, adapted, or intended for producing abortion." For the past half century, courts have not had the occasion to elaborate further on the meaning of the Comstock Act as it relates to abortion, including regarding

[19] Although the 1971 Congress eliminated the preexisting broad prohibitions on sending contraception-related articles and information using the mails or common carriage, it added a narrower prohibition designed to prevent the mailing of unsolicited contraceptive items and advertising to private homes. *See* 39 U.S.C. § 3001(e); *see also* 18 U.S.C. § 1461 (making it a crime to knowingly use the mails to mail anything deemed "nonmailable" in section 3001(e)). In *Bolger*, the Supreme Court held that the ban on unsolicited advertisements of contraceptives violates the First Amendment. 463 U.S. at 61.

the sources of law that inform whether an abortion would be "unlawful" for purposes of the established construction of the Act.

II.

In Part I we demonstrated that, in accord with the prevailing judicial construction Congress ratified, section 1461 does not prohibit the mailing of articles that can be used to produce abortion, including mifepristone and misoprostol, where the sender lacks the intent that those items should be used unlawfully.[20] We turn now to address the many circumstances in which a sender of these drugs typically will lack an intent that they be used unlawfully.

Federal law does not prohibit the use of mifepristone and misoprostol for producing abortions. Indeed, the FDA has determined the use of mifepristone in a regimen with misoprostol to be safe and effective for the medical termination of early pregnancy. And, to the extent relevant, these drugs can serve important medical purposes and recipients in every state can use them lawfully in some circumstances. This is true even when the drugs would be delivered to an address in a jurisdiction with restrictive abortion laws, because women who receive the drugs in all fifty states may, at least in some circumstances, lawfully use mifepristone and misoprostol to induce an abortion.

We note that those sending or delivering mifepristone and misoprostol typically will lack complete knowledge of how the recipients intend to use them and whether that use is unlawful under relevant law. Therefore, even when a sender or deliverer of mifepristone or misoprostol, including USPS, knows that a package contains such drugs—or indeed that they will be used to facilitate an abortion—such knowledge alone is not a sufficient basis for concluding that section 1461 has been violated. We also recognize that USPS may have reason to consider adopting uniform policies or practices regarding the mailing of mifepristone or misoprostol. *Cf. Smith v. United States*, 431 U.S. 291, 304 n.10 (1977) ("[T]he nationwide character of the postal system argues in favor of a nationally uniform construction of [section] 1461.").

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[20] *See supra* note 3 (noting that the same test would apply to section 1462 and to recipients of the drugs to the extent those persons might be amenable to prosecution).

We have not undertaken the challenging task of a detailed review of state abortion laws, but we can offer some illustrative uses for mifepristone and misoprostol that the law of a given state would not prohibit:

- First, in most states—where a majority of the U.S. population lives—abortion continues to be lawful until at least twenty weeks' gestation. It is very unlikely that someone sending validly prescribed mifepristone or misoprostol into such states will intend for them to be used unlawfully.
- Second, even some states that in recent months have enacted or begun to enforce more restrictive abortion laws continue to allow abortion for at least some number of weeks of pregnancy. Use of mifepristone and misoprostol to terminate a pregnancy that falls within that period would be lawful.
- Third, thus far, no state that has enacted or newly begun to enforce restrictions on abortion in the wake of *Dobbs v. Jackson Women's Health Organization*, 142 S. Ct. 2228 (2022), prohibits abortions that are necessary to preserve the life of the woman.[21] Many medical conditions that make pregnancy potentially life-threatening—for instance, certain heart conditions, pulmonary hypertension, or Marfan Syndrome[22]—are known in the first trimester, when women most commonly use mifepristone and misoprostol to induce an abortion. Such a use of these drugs to terminate a life-threatening pregnancy would be lawful.
- Fourth, some state abortion restrictions also include exceptions for cases of rape or incest, to protect the health of the woman, or where there are severe fetal anomalies. The use of mifepristone or miso-

[21] *See Dobbs*, 142 S. Ct. at 2305 n.2 (Kavanaugh, J., concurring) ("Abortion statutes traditionally and currently provide for an exception when an abortion is necessary to protect the life of the mother."); *see also Roe*, 410 U.S. at 173 (Rehnquist, J., dissenting) ("[I]f [a state] statute were to prohibit an abortion even where the mother's life is in jeopardy, I have little doubt that such a statute would lack a rational relation to a valid state objective . . . .").

[22] *See, e.g.*, Inst. of Med., Clinical Prevention Services for Women: Closing the Gaps 103–04 (2011); *see also Burwell v. Hobby Lobby Stores, Inc.*, 573 U.S. 682, 737 (2014) (Kennedy, J., concurring) (noting that "[t]here are many medical conditions for which pregnancy is contraindicated").

prostol to produce an abortion in such cases would therefore be lawful.

- Fifth, some states that regulate the conduct of certain actors involved in abortions do not make it unlawful for the woman herself to abort her pregnancy. In those contexts, section 1461 might not prohibit the mailing of mifepristone and misoprostol to a woman in a state with restrictions on abortion, even if the sender does so with the intent that the woman use the drugs to produce an abortion.
- Sixth, even if a state prohibits a pregnant person from ingesting mifepristone or misoprostol for the purpose of inducing an abortion, such an individual has a constitutional right to travel to another state that has not prohibited that activity and to ingest the drugs there.[23] Someone sending a woman these drugs is unlikely to know where she will use them, which might be in a state in which such use is lawful.
- Seventh, federal agencies provide abortion services in some circumstances without regard to contrary state law.[24] Mailings of abortion

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[23] *See Dobbs*, 142 S. Ct. at 2309 (Kavanaugh, J., concurring) ("[M]ay a State bar a resident of that State from traveling to another State to obtain an abortion? In my view, the answer is no based on the constitutional right to interstate travel."); *id.* (referring to the question as "not especially difficult"); *see also Bigelow v. Virginia*, 421 U.S. 809, 824 (1975) (explaining that Virginia could not "prevent its residents from traveling to New York to obtain [abortion] services or . . . prosecute them for going there" (citing *United States v. Guest*, 383 U.S. 745, 757–59 (1966))).

[24] The Department of Veterans Affairs ("VA"), for example, recently has begun providing abortions to veterans and certain other VA beneficiaries without regard to state law when the life or health of the woman would be endangered if the pregnancy were carried to term or the pregnancy is the result of an act of rape or incest. *See* Reproductive Health Services, 87 Fed. Reg. 55,287, 55,288 (Sept. 9, 2022). "[S]tates may not restrict VA and its employees acting within the scope of their federal authority from providing abortion services as authorized by federal law, including VA's rule." *Intergovernmental Immunity for the Department of Veterans Affairs and Its Employees When Providing Certain Abortion Services*, 46 Op. O.L.C. __, at *10; *see also* 87 Fed. Reg. at 55,294 (noting that state and local laws, including criminal laws, that "restrict[], limit[], or otherwise impede[] a VA professional's provision of care permitted by" this new rule "would be preempted" (citing 38 C.F.R. § 17.419(b))). Also, the Department of Defense ("DoD") has for many years provided service members, dependents, and other beneficiaries of DoD health care services with abortion services when a pregnancy is the result of rape or incest or when continuing the pregnancy would endanger the woman's life, and DoD has indicated it will continue to do so without regard to contrary state laws. *See*

medications intended to be used pursuant to these federal authorities would be lawful under section 1461, because contrary state law could not constitutionally be applied.

- Finally, individuals use mifepristone and misoprostol for medical purposes other than to induce abortions and the legality of those uses would remain unaffected by state restrictions on abortion. For instance, the same dosages of mifepristone and misoprostol that are used for medication abortion can be used to treat a miscarriage,[25] and misoprostol is commonly prescribed for the prevention and treatment of gastric ulcers.[26]

Thus, no matter where the drugs are delivered, a variety of uses of mifepristone and misoprostol serve important medical purposes and are lawful under federal and state law. Accordingly, USPS could not reasonably assume that the drugs are nonmailable simply because they are being sent into a jurisdiction that significantly restricts abortion. Nor would such an assumption based solely on the recipient's address be reasonable even if it is apparent that some women in a particular state are using the drugs in question in violation of state law. *Cf. Youngs Rubber*, 45 F.2d at 110 (although the volume of the plaintiff's sales nationwide justified an inference that the drug stores to which the condoms were being delivered must have been selling at least some of them for purposes that were prohibited under state law—"and that plaintiff must know this"—that was insufficient to conclude that the company intended such illegal conduct by the recipients).

In conclusion, section 1461 does not prohibit the mailing of mifepristone or misoprostol where the sender lacks the intent that the recipient will use them unlawfully. And in light of the many lawful uses of mifepristone and misoprostol, the fact that these drugs are being mailed to a

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Memorandum for Senior Pentagon Leadership from Gilbert R. Cisneros, Jr., Under Secretary of Defense for Personnel and Readiness, Department of Defense, *Re: Ensuring Access to Essential Women's Health Care Services for Service Members, Dependents, Beneficiaries, and Department of Defense Civilian Employees* (June 28, 2022).

[25] *See, e.g.*, Honor Macnaughton, Melissa Nothnagle & Jessica Early, *Mifepristone and Misoprostol for Early Pregnancy Loss and Medication Abortion*, 103 Am. Fam. Physician 473, 475 (Apr. 15, 2021).

[26] *See Cytotec Misoprostol Tablets*, U.S. Food & Drug Admin. 5–6 (Aug. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019268s051lbl.pdf (misoprostol label).

jurisdiction that significantly restricts abortion is not a sufficient basis for concluding that the mailing violates section 1461.[27]

CHRISTOPHER H. SCHROEDER
Assistant Attorney General
Office of Legal Counsel

[27] While this request was pending, we received a similar request from the Department of Health and Human Services ("HHS") regarding the Comstock Act in connection with the Food and Drug Administration's Risk Evaluation and Mitigation Strategy for mifepristone. We conveyed our conclusions by e-mail to HHS on December 19, 2022, and we noted there that this memorandum was forthcoming. E-mail for Samuel Bagenstos, General Counsel, HHS, from Christopher H. Schroeder, Assistant Attorney General, Office of Legal Counsel, *Re: Advice Regarding Comstock* (Dec. 19, 2022, 8:31 PM).

Exhibit 1D

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 mifepristone 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 they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

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

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

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

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

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

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

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

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

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

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

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or 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: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

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

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

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone 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 they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

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.

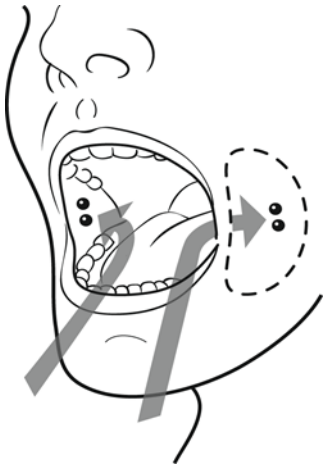
Remove any intrauterine device (“IUD”) before treatment with MIFEPREX begins [*see Contraindications (4)*].

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 them to be when taking 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 the patient 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.

Patients 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, patients 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. Patients 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 them 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 adrenal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute adrenal 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 patients 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 Mifepristone REMS Program

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

Notable requirements of the mifepristone 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 only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

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.

Patients 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 U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. 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 patients 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	# 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

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-U.S. Clinical Studies

Adverse Reaction	U.S.			Non-U.S.		
	# 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

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

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

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

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone,fetal losses were much higher than in control animals. Skull 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.

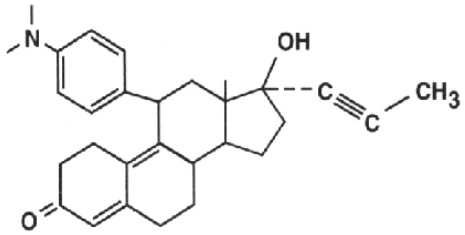
10 OVERDOSAGE

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, the patient should be observed closely for signs of adrenal failure.

11 DESCRIPTION

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

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

of prostaglandins.

12.2 Pharmacodynamics

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

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

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

12.3 Pharmacokinetics

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

Absorption

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

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

Distribution

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

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

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

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

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

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

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

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone 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 Mifepristone REMS Program [*see Warnings and Precautions (5.3)*]. Under the mifepristone REMS Program:
    - Patients must sign a Patient Agreement Form.
    - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

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 the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever *[see Boxed Warning]*.
-

Compliance with Treatment Schedule and Follow-up Assessment

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

01/2023

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.

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 patients 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 or pharmacy.
- 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.

24 to 48 hours after taking Mifeprex:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.

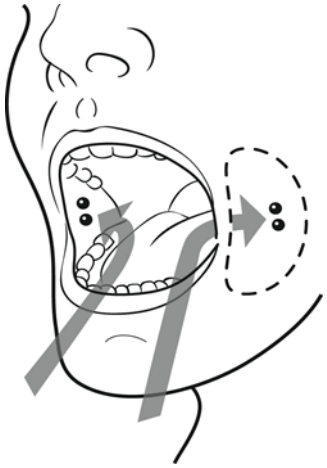


Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

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

When should I begin birth control?

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

What should I avoid while taking Mifeprex and misoprostol?

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

What are the possible side effects of Mifeprex and misoprostol?

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

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

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

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

General information about the safe and effective use of Mifeprex.

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

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

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

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 01/2023

Exhibit 1E

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

MEDICAL REVIEW(S)

JAN 27 2000

MEDICAL OFFICER'S REVIEW OF AMENDMENTS 024 AND 033
FINAL REPORTS FOR THE U.S. CLINICAL TRIALS INDUCING ABORTION UP TO 63 DAYS GESTATIONAL AGE AND COMPLETE RESPONSES REGARDING DISTRIBUTION SYSTEM AND PHASE 4 COMMITMENTS

NDA Number: 20-687

Applicant: Population Council
One Dag Hammarskjold Plaza
New York, New York 10017

Dates of Submission: June 3, 1999 and August 18, 1999

Dates Submissions Received: June 4, 1999 and August 19,1999

Date Review Completed: October 28, 1999

Date Review Revised: November 19, 1999

Date Review Finalized: November 22,1999

I. General Information:

A. Name of Drug:
1. Established Name: Mifepristone
2. Trade Name: None designated as yet.

3. Laboratory Code Name: RU 38486 (RU-486).

B. Pharmacologic Category: Antiprogestational and antiglucocorticoid agent.

C. Proposed Indication: Medical termination of intrauterine pregnancy through 49 days' pregnancy.

D. Dosage Form and Route of Administration: Tablet for oral administration.

E. Strength: Each tablet contains 200 mg of mifepristone.

F. Dosage: Three 200 mg tablets (600 mg) of mifepristone are taken as a single oral dose. Unless abortion has occurred, the patient takes two 200 μg tablets (400 μg) of misoprostol orally two days after ingesting mifepristone.

G. Related Drugs: None marketed.

H. Table of Contents:

II. Manufacturing Controls: Please refer to chemist's review for details.

III. Pharmacology and Pharmacodynamics: Please refer to pharmacologist's review for details.

IV. Clinical Background:

Mifepristone is a synthetic steroid that was approved for the termination of pregnancy in France in December 1988 (launched September 1989), in Sweden in 1992, in the United Kingdom in 1991, and in China in 1988. (It should be noted that mifepristone used in China is not manufactured by Roussel Uclaf but by domestic companies). When administered alone in total doses of 1400-1600 mg over 1-10 days, the success rate was 64-85%. Subsequent studies demonstrated that the administration of mifepristone followed by a synthetic prostaglandin analog increases the success rate to over 95%. In a preliminary study of 100 women, the success rate of 600 mg mifepristone and 0.2 mg misoprostol was 95% for pregnancies of no more than 49 days of amenorrhea. Misoprostol is a synthetic prostaglandin E_1 analog

In the misoprostol

Nine phase 2 clinical studies to determine the most effective dose and dosage regimen for mifepristone used alone for the interruption of pregnancy were conducted in France between 1983 and 1986. Patients in these studies were entered with a target gestational age of less than or equal to 41 days of amenorrhea. One thousand patients were exposed to doses ranging from 100 mg for one to four days to 800 mg for one day.

Following completion of the phase 2 studies, nine phase 3 clinical trials employing a single 600 mg dose of mifepristone were conducted to evaluate the efficacy and the

safety of this dose. The target population was patients with pregnancies having a gestational age ≤42 days of amenorrhea. A total of 2,459 patients were studied.

The advantage of combining mifepristone 600 mg with a prostaglandin (sulprostone 250μg I.M. 36-48 hours later) for pregnancy interruption was demonstrated in 1985. A series of ten clinical trials were conducted between 1987 and 1991 to confirm and extend these initial observations. In addition to sulprostone, other prostaglandins including gemeprost, 15MePGF 2a, and prostine E_2 were evaluated. During the ten studies, a total of 19,947 patients were exposed to mifepristone administered as a single 600 mg dose. One of these studies enrolled over 16,000 patients. Very rare cases of hypotension and one myocardial infarction were reported. Successful termination of early pregnancy was achieved in 82.6 to 100% of the patients enrolled in these studies and the safety of mifepristone was confirmed.

The efficacy and safety of mifepristone given as a single 600 mg oral dose in combination with misoprostol 0.4 mg orally administered approximately 36 to 48 hours after mifepristone for termination of pregnancy was evaluated in two historically controlled, pivotal clinical trials conducted in France. The first study included women with intrauterine pregnancies of ≤ 49 days and the second study included women with intrauterine pregnancies of ≤63 days. In the second study, a second dose of 200 μg of misoprostal was given 3 hours after the first dose if complete abortion had not occurred. In the first study of 1205 evaluable patients, the complete abortion rate was 95.4% and in the second study of 1104 evaluable patients, the complete abortion rate was 92.8%. These two studies were evaluated in the review of a new drug application that was submitted March 16, 1996.

V. Regulatory Background:

2 **Page(s) Redacted**

Deliberative Process

VI. Statistical Consultation: None required

VII. Clinical Studies:

The efficacy and safety of mifepristone was evaluated in two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols (166A and 166B) at 17 centers (University hospitals, Planned Parenthood clinics, and free-standing clinics). The studies were conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

Data from the two studies were combined in the following evaluation.

A. Investigators:

Dr. Paul Blumenthal	Baltimore, Maryland
Dr. Lynn Borgatta	White Plains, New York
Dr. Mitchell Crenin	Pittsburgh, Pennsylvania
Dr. Catherine Dean	St. Louis, Missouri
Dr. Susan Haskell	Des Moines, Iowa
Dr. Tyrone Mallory	Atlanta, Georgia
Dr. Daniel Mishell, Jr.	Los Angeles, California
Dr. Mark Nichols	Portland, Oregon
Dr. Alfred Poindexter	Houston, Texas
Dr. Suzanne Poppema	Seattle, Washington

Dr. Eugene Rothenberg	Shrewsbury, New Jersey
Dr. Katherine Sheehan	San Diego, California
Dr. Laszlo Sogor	Cleveland, Ohio
Dr. Judith Tyson	Burlington, Vermont
Dr. Peter Vargas	Aurora, Colorado
Dr. Carolyn Westhoff	New York, New York

B. Objectives of the Study:

The study was conducted to evaluate the effectiveness, safety, acceptability, and feasibility of using mifepristone and misoprotol in a variety of clinical settings within the United States health care system for the induction of abortion in women whose duration of amenorrhea was no more than 63 days.

C. Rationale for the Study:

Extensive experience has been gained outside the United States with the use of mifepristone and various prostaglandin analogs, including misoprostol, for the termination of pregnancies up to 63 days, with complete abortion rates ranging from 92.7% to 99%. The applicant wished to confirm the efficacy and safety of the regimen in the United States.

D. Method of Assignment to Treatment:

Eligible patients fulfilling all of the inclusion criteria and none of the exclusion criteria were assigned to one of the three treatment groups, based on gestational age.

E. Number of Subjects:

A total of 2,121 patients were enrolled including 859 patients in groups 1,722 patients in group 2, and 540 patients in group 3.

F. Duration of Clinical Trial:

Patients were to receive mifepristone on day 1 and misoprostol on day 3 and were to be observed in the clinical setting for at least 4 hours after misoprostol administration. Patients were to return for evaluation on day 15.

G. Inclusion Criteria:

1. Was at least 18 years of age and in good general health.

2. Requested a voluntary termination of pregnancy.

3. Had a positive urine pregnancy test.

4. Had an intrauterine pregnancy with a duration of amenorrhea of ≤63 days (from the first day of her last menstrual period) that was confirmed by uterine size on pelvic examination and by vaginal ultrasound evaluation.

5. Agreed to have a surgical termination of pregnancy if the study procedures failed to terminate her pregnancy.

6. Was a resident of the United States.

7. Gave written informed consent to participate in the study and was willing and able to participate.

H. Exclusion Criteria:

1. Had evidence of any disorder which represented a contraindication to the use of mifepristone (such as adrenal disease or a condition requiring chronic corticosteroid administration) or misoprostol (such as asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or a known allergy to prostaglandins).

2. Had a history of severe liver, respiratory, or renal disease or thromboembolism.

3. Had a cardiovascular disease, e.g. angina, valve disease, arrhythmia, cardiac failure, or insulin dependent diabetes.

4. Had hypertension that was being treated on a chronic basis or had blood pressure of greater than 140/90mmHg.

5. Was anemic (hemoglobin < 10 g/dL or hematocrit < 30%).

6. Had a known clotting defect or was receiving anticoagulants.

7. Had an IUD *in situ*.

8. Was breastfeeding.

9. Had adnexal masses or tenderness on pelvic examination that suggested pelvic inflammatory disease.

10. Had an ectopic pregnancy or threatened abortion.

11. Was over 35 years of age and smoked more than 10 cigarettes per day, and

had another risk factor for cardiovascular disease such as diabetes mellitus, hyperlipidemia, hypertension, or a family history of ischemic heart disease.

12. Was unlikely to understand and comply with the requirements of the study.

13. Lived or worked more than one hour from the emergency care facility that served the abortion center.

I. Trial Period:

September 13, 1994 to September 12, 1995

J. Dosage and Mode of Administration:

Patients were not to eat during the one hour before and after the administration of mifepristone. In the presence of the investigator, each patient was administered three 200 mg mifepristone tablets by mouth with no more than 240 mL of water. Patients were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Unless the investigator could verify unequivocally that complete abortion had occurred, patients were administered two 200 μg misoprostol tablets by mouth with no more than 240 mL of water in the presence of the investigator 36 to 60 hours after the administration of mifepristone.

K. Efficacy Assessments:

Pelvic examinations were performed before mifepristone administration at visit 1, before misoprostol administration at visit 2, during the 4 hour observation period after misoprostol administration, and at the visit 3 evaluation. At visit 1, patients also had transvaginal ultrasound examinations and quantitative hCG β subunit pregnancy tests performed. At visits 2 and 3, ultrasound examinations were performed at the discretion of the investigator.

The outcome of treatment was classified as follows:

1. Complete abortion: pregnancy termination and complete expulsion of the products of conception without the need of surgical intervention.

2. Incomplete abortion: pregnancy termination with either partial expulsion or nonexpulsion of the products of conception diagnosed at visit 3 or at study end if later than visit 3 with surgery required.

3. Ongoing pregnancy: a viable pregnancy diagnosed at visit 3 based on fetal heartbeat and/or fetal growth indicating gestations that are

two weeks older than at visit 1; surgery required.

4. Medical intervention: before visit 3, the investigator judged that a surgical intervention was medically indicated.

5. Patient request: before visit 3, the patient chose not to proceed with the medical method of abortion and requested surgical intervention.

In the analyses of treatment outcome, complete abortion only was classified as a treatment success. All other categories resulted in a surgical procedure and , therefore, were classified as treatment failures.

L. Safety Assessments:

Adverse events were summarized and evaluated.

M. Disposition of Patients:

A total of 2121 patients were enrolled. Of these, 2015 (95.0%) were included in the efficacy analyses. There were 106 patients excluded from the efficacy analyses because of failure to show up for visit 3, thus preventing confirmation of a final outcome. For 92 of these patients, there was some information suggesting a successful outcome. For one excluded patient, there was evidence that suggested failure. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. All 2121 patients were evaluable for safety. A total of 827 patients in Group 1, 678 patients in Group 2, and 510 patients in Group 3 were included in the efficacy evaluation.

N. Demographic Characteristics:

Most patients were Caucasian (71%), 20-29 years of age (61%; mean age of 26.9 years), of normal body mass index (71%), nulliparous (55%) and had a previous elective abortion (51%). The differences among the three gestational age groups in race distribution and mean age, weight, and body mass index were small and not of clinical significance.

O. Results:

1. Efficacy:

Success and failure rates are summarized in Table 1.

Table 1
(Sponsor's Table 4.1)
Treatment Outcomes by Gestational Age (Evaluable Patients)

Treatment Outcomes	Group 1 ≤ 49 days N = 827	Group 2 50-56 days N = 678	Group 3 57-63 days N = 510
Total Successes	762 (92%)	563 (83%)	395 (77%)
RU-486 alone	40 (5%)	12 (2%)	4 (< 1%)
Plus misoprostol	722 (87%)	551 (81%)	391 (77%)
Total Failures	65 (8%)	115 (17%)	115 (23%)
Med intervention	13 (2%)	26 (4%)	21 (4%)
Patient request	5 (< 1%)	13 (2%)	12 (2%)
Incomplete ab	39 (5%)	51 (8%)	36 (7%)
Ongoing preg	8 (< 1%)	25 (4%)	46 (9%)

Failures are discussed in this review in the "Safety" section of "Results."

Complete abortion rates according to time of occurrence are displayed in Table 2 as confirmed by the investigators.

Table 2
(Sponsor's Table 5.1)
Time to Occurrence of Complete Abortion

Occurrence Time	Group 1 ≤ 49 days N =827	Group 2 50-56 days N=678	Group 3 57-63 days N=510
Mifepristone alone	40 (4.8%)	12 (1.8%)	4 (0.8%)
≤ 4h after misoprostol	376 (45.5%)	312 (46.0%)	178 (34.9%)
> 4h & < end of day 4	178 (21.5%)	118 (17.4%)	118 (23.1%)
After day 4	168 (20.3%)	121 (17.8%)	95 (18.6%)
Surgical intervention	65 (7.9%)	115 (17.0%)	115 (22.5%)

2. Safety:

Adverse events, regardless of causality, were reported for at least 99% of the patients in each gestational age group. More than one adverse event was reported for most patients. The majority of adverse events were of mild or moderate severity. Approximately 23% of the adverse events in each gestational age group were judged to be severe. The most common adverse event was abdominal pain, including uterine cramping. This was to be expected since the treatment procedure is designed to induce the uterine cramping (and bleeding) necessary to produce an abortion.

Other commonly reported adverse events were nausea, vomiting, headache, diarrhea, and dizziness. No serious adverse events were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. Table 3 shows that the rates of most, but not all, adverse events that occurred in patients whose gestational age was ≤ 49 days were not significantly different from the rates across all gestational age groups.

Table 3

Most Commonly Reported Adverse Events

Adverse Event	Group 1 ≤ 49 days N=859 Percentage	Groups 1, 2, and 3 ≤ 63 days N=2121 Percentage
Abdominal pain (cramping)	96	97
Nausea	61	67
Headache	31	32
Vomiting	26	34
Diarrhea	20	23
Dizziness	12	12
Fatigue	10	9
Back pain	9	9
Uterine hemorrhage	5	7
Fever	4	4
Viral infections	4	4
Vaginitis	3	4
Rigors (chills/shaking)	3	3
Dyspepsia	3	3
Insomnia	3	2
Asthenia	2	2
Leg pain	2	2
Anxiety	2	2
Anemia	2	2
Leukorrhea	2	2
Sinusitis	2	2
Syncope	1	2

Table 4 shows the rates of adverse events in any gestational age group which were significantly different across gestational age groups.

Table 4
Adverse Events Significantly Different Across Gestational Age Groups

Adverse Event	Group 1 ≤ 49 days Percentage	Group 2 50-56 days Percentage	Group 3 57-63 days Percentage
Nausea	61	71	72
Vomiting	26	38	41
Diarrhea	20	23	26
Uterine hemorrhage	5	8	10

No patient was discontinued from the study because of an adverse event and there were no deaths.

The median bleeding duration for group 1 was 14 days and 15 days for groups 2 and 3.

The proportions of patients who received any medications for bleeding increased with increasing gestational age form 5.7% in group 1 to 10.7% in group 3. A total of 146 patients (6.9%) received uterotonics (ergot-type medications or oxytocin) for bleeding.

Fourteen patients (0.7%) were hospitalized for an adverse event. Of these patients, 2 of 4 in the ≤ 49 days group, 3 of 5 in the 50-56 days group, and 3 of 5 in the 56-63 days group had adverse events (severe excessive bleeding) which were considered to be study drug related. The other patients were hospitalized for reasons unrelated to study treatment (pneumonia, meningitis, automobile accident, depression, shooting injury, endometritis).

Nineteen patients (0.9%) had emergency room visits that did not result in hospitalization. Sixteen of these 19 patients had excessive bleeding (2, ≤ 49 days; 7, 50-56 days; 7, 57-63 days). The other three visits were for chest pain, nausea and vomiting, and cramping.

Four patients received blood transfusions (1, ≤ 49 days; 2, 50-56 days; 1, 57-63 days). Three of these patients were hospitalized.

IV fluids were administered for various reasons to 9 (1.0%) patients in the ≤ 49 days group, 19 (2.6%) in the 50-56 days group, and 18 (3.3%) in the 57-63 days group.

The following five potentially serious adverse events occurred:

A 34 year old patient with a 20 year history of seizures and a pregnancy of

46 days gestational age had a mild seizure (convulsion) on the day of mifepristone administration and received 250 mg of dilantin. In the opinion of the investigator, the patient's seizure was not related to treatment with mifepristone and she received misoprostol 47 hours after the mifepristone.

A 28 year old of 54 days gestational age with a negative gastrointestinal history reported possible blood in her stool a month after misoprostol administration. In the opinion of the investigator, the patient's melena was not related to study treatment.

A 23 year old of 57 days gestational age developed moderate purpura (body bruises) that lasted for one day without treatment ten days after receiving misoprostol. In the opinion of the investigator, the patient's purpura was not related to study treatment.

A 21 year old of 57 days gestational age developed severe viral meningitis 6 days after receiving misoprostol and was hospitalized. In the opinion of the investigator, the patient's meningitis was not related to study treatment.

A 27 year old of 60 days gestational age with a negative gastrointestinal history reported blood in her stool 3 days after receiving misoprostol. At the time of last contact with the patient three weeks later, no further incidents of melena had been reported. In the opinion of the investigator, the patient's melena was not related to study treatment.

The proportions of patients with a decrease in hemoglobin or hematocrit of more than 20% from their pre-mifepristone administration levels increased significantly with increasing gestational age, from 3.1% in the ≤ 49 days group to 8.0% in the 57-63 days group.

Of the 1028 patients with hemoglobin measurements before and after misoprostol administration, 131 had a decrease of at least 2mg/dL (7.8%, ≤49 days; 15.0%, 50-60 days; 17.4% 57-63 days).

Hypotension after administration of misoprostol occurred in 0.3% - 1.4% of all treated patients.

Hypertension after administration of misoprostol occurred in 1.5% - 1.7% of all treated patients.

Decrease in heart rate by > 20% after administration of misoprostol occurred in 18.2% - 21.3% of all patients.

Increase in heart rate by >20% after administration of misoprostol occurred in 11.8% - 14.1% of all patients.

For the subgroup of patients with a full panel of laboratory tests, the median changes were small and not of clinical significance.

Failure of the mifepristone - misoprostol procedure required surgical intervention which is an additional safety concern, albeit small. A total of 295 patients were classified as having failed medical abortion. Of these patients, 79 (27%) had ongoing pregnancies, 126 (43%) had incomplete abortions, 30 (10%) requested and had surgical terminations, and the remaining 60 (20%) patients had surgical terminations performed because of medical indications directly related to the medical procedure. In group 1 (≤ 49 days gestation), of the 65 failures, 8 (12%) patients had ongoing pregnancies, 39 (60%) patients had incomplete abortions, 5 (8%) requested and had surgical terminations performed, and the remaining 13 (20%) patients had surgical terminations directly related to the medical procedure. The failure rates for medical intervention, patient request, incomplete abortion, and ongoing pregnancy were significantly higher in groups 2 and 3 than in group 1.

For each gestational age group, the adverse event rates were highest at Planned Parenthood clinics and lowest at Free-Standing clinics, with university hospital clinics in the middle.

VIII. Reviewer's Comments, Evaluation, and Conclusions:

Two studies were conducted according to two identical protocols at 17 centers to evaluate a mifepristone - misoprostol regimen for the termination of pregnancies in the United States health care system. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤ 49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

The studies included women who requested a voluntary termination of pregnancy, had a positive pregnancy test, and a documented intrauterine pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than ten cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had intrauterine devices, were breast-feeding, were receiving anticoagulation or long-term glucocorticoid therapy, had adrenal masses, had

ectopic pregnancies, or had signs or symptoms suggesting that they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. A total of 2,121 women were enrolled in the two studies including 859 women who were in the ≤ 49 days group, which is the gestational age which is the subject of this application.

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography and women were assigned to the appropriate gestational age group.

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took three 200 mg tablets of mifepristone orally in the presence of the investigator. Patients did not eat for one hour before and after the consumption of the mifepristone. At visit 2 (day 3), they took 400 μg of misoprostol orally unless a complete abortion had already occurred. Patients did not smoke during the 48 hours following mifepristone consumption and on the day misoprostol was administered. Patients then remained at the clinics under observation for at least four hours. Adverse events such as nausea, vomiting, diarrhea, abdominal pain, and vaginal bleeding were rated by the women and recorded. Blood pressure and heart rate were measured at least hourly. Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 as "spotting", "normal", or "heavy." During this period, the women were also monitored for the expulsion of the conceptus. At visit 3 (day 15), the treatment outcome was assessed.

Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure. The need for a vacuum aspiration or dilatation and curettage constituted a failure. A surgical procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. The efficacy analysis, therefore, included 2015 women. No additional information is available on the outcomes of the 5 women with continuing pregnancies who were lost to followup. All other women with continuing pregnancies were aborted surgically.

Efficacy was 92% in the ≤ 49 days group with a lower 95% confidence interval of 90%. This is somewhat less than the 95.5% efficacy with a lower 95% C.I. of 94.2% reported in the pivotal French studies upon which approval of this application was recommended.

Efficacy was 83% in the 50-56 days group with a lower 95% confidence interval of 80%. Efficacy was 77% in the 57-63 days group with a lower 95% confidence interval of 74%.

The 92% success rate in the ≤ 49 days group is an acceptable one.

The median duration of bleeding in the ≤ 49 days group was 14 days. The average duration of bleeding was 16 days. This is considerably longer than the average duration of 9 days reported in the French studies upon which approval of this application was recommended, but is an acceptable duration.

Excessive bleeding necessitated blood transfusion in only 1 patient in the ≤ 49 days group and required hospitalization of only 2 patients in the ≤ 49 days group. An additional 2 patients in the ≤ 49 days group were treated in the emergency room for excessive bleeding. Thirteen (2%) patients in the ≤ 49 days group required surgical intervention because of excessive bleeding. Bleeding was managed by the administration of uterotonic agents such as oxytocin, methylergonovine or vasopressin in 5% of patients in the≤ 49 days group.

The adverse event rates were higher in these studies than those in the pivotal French studies upon which approval of this application was recommended. This is shown in Table 5.

Table 5

Frequent Adverse Events (≤ 49 days) in French and U.S. Trials

Adverse Event	French Trials	U.S. Trials
Abdominal pain (cramping)	83%	96%
Nausea	43%	61%
Headache	2%	31%
Vomiting	18%	26%
Diarrhea	12%	20%
Dizziness	1%	12%

The majority of adverse events were of mild or moderate severity. The difference in the frequency of common adverse events noted above is acceptable.

In the pivotal French trials, 5.5% of subjects had a decrease in hemoglobin of greater than 2g/dL while in the U.S. trials, 7.8 % of patients in the ≤ 49 days group had such a decrease. This difference is an acceptable one.

The U.S. clinical trials confirmed the findings of the pivotal French trials that mifepristone and misoprostol are safe and effective in terminating pregnancies of up to 49 days gestation even though the success rate in the U.S. trials was lower

than that of the French trials. This lower success rate might be related to the lack of experience of most of the U.S. investigators with medical abortion. The lower success rate might also be attributable somewhat to the fact that in the U.S. trials, a woman's request for a surgical termination any time after receiving mifepristone was honored and classified as a failure rather than being excluded form the efficacy analysis. However, in the ≤ 49 days group, less than 8% of the failures (5 patients) were because of patient requests.

The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age. The majority of surgical interventions were for incomplete abortion and excessive bleeding.

This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.

Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility including at least a four hours stay after the administration of the misoprostol.

In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects).

In the U.S. clinical trials, an increase in the incidence of some adverse events (vomiting, nausea, diarrhea, uterine hemorrhage) occurred in the 50-56 and 57-63 days gestational age groups compared to the ≤ 49 days group. The safety profile of the ≤ 49 days group in the U.S. study did not differ significantly from the pivotal French studies, even though the incidence of common adverse events in the U.S. clinical trials was higher than that of the French trials in the ≤ 49 days group. The percentage of patients in the U.S. studies and the French studies requiring hospitalization, requiring blood transfusion and experiencing heavy bleeding was about the same. However, about 1.6% of the patients in the ≤ 49 days group in the U.S. study had surgical intervention because of heavy bleeding compared to less than 1% of patients in the French studies. The average duration of bleeding was 16 days in the U.S. studies compared to 9 days in the French studies.

While the U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical

abortions with gestations of 49 days duration or less, they demonstrate that with longer durations of gestation (50-56 days and 57-63 days), the treatment regimen is less effective and the incidence of adverse events is higher.

A comparison of medical termination of pregnancy with surgical termination is of interest in a polulation of women who are given a choice to select between medical and surgical termination of early pregnancy. Such a comparative clinical trial was conducted according to a uniform protocol from 1991 to 1993 in urban clinics in China, Cuba, and India, three countries where abortion is legal and available. A total of 1373 women with amenorrhea ≤ 56 days were given a choice of surgical abortion or mifepristone and misoprostol in the same dosage regimen as used in the U.S. studies. The results of this study were published in 1997. The medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion (8.6% versus 0.4% in China, 16.0% versus 4.0% in Cuba, and 5.2% versus 0% in India). In each site failure rates of medical abortion increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients. The only serious complication was excessive bleeding in medical abortion patients, which is a reason for surgical intervention and for dissatisfaction among medical abortion patients. Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients. Slightly higher proportions of medical than surgical patients were dissatisfied (8.8% versus 3.8%). Despite the bleeding pattern and the failure rate of the medical abortion method, particularly in China, medical abortion by the mifepristone and misoprostol regimen was said by the authors of this published study to be safe, efficacious, and highly desired by and acceptable to women in developing countries.

The results of a smaller study published in 1999 comparing mifepristone to surgical abortion in U.S. women are consistent with the findings of the larger comparative clinical trial done in China, Cuba, and India. The study was a nonconcurrent, prospective, cohort analysis of 178 mifepristone - misoprostol and 199 suction curettage abortion subjects with intrauterine pregnancies ≤ 63 days gestational age. The medical abortion cohort represents all of the subjects enrolled at one U.S. clinical site for the mifepristone clinical trial between December, 1994 and August, 1995. The surgical abortion cohort was enrolled prospectively at the same clinical site between November, 1995 and December, 1996. Overall, 18.3% of medical and 4.7% surgical patients failed their primary procedure and received an unanticipated suction curettage (R.R. 3.93; 95% CI 1.87,8.29). The risk of failure demonstrated a statistically significant upward trend from 3.3 to 4.4 with advancing gestational age. Four mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine

mifepristone patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the mifepristone group than in the surgical group (35 days versus 8 days). Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients. The mean difference in bleeding days between cohorts was 9.6 days (95% CI, 6.8, 12.4). Mifepristone patients reported significantly longer bleeding in all three gestational age groups. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients. The use of antiemetic agents during the abortion procedure was significantly more common in mifepristone patients than surgical patients (31.1% versus 1%). Mifepristone patients were routinely offered oral narcotics for expulsion-related pain, and 78.5% used them. Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients (RR 7.4, 95% CI 4.7, 11.5). Nausea or vomiting in the follow-up interval was common in the mifepristone group (68.6%), but rare among surgical patients (0.6%) (RR 117.9, 95% CI 16.7, 834.7).

Although the mifepristone and surgical abortion techniques are both safe and effective, the abortion and post-abortion experiences differ significantly as reported in the two published studies above that permit direct comparison of the two techniques in a prospective manner.

IX. Labeling Evaluation:

Comments regarding labeling revisions were transmitted to the sponsor in a letter dated September 18, 1996. Revised draft labeling was submitted by the sponsor June 25, 1999 and currently is under review.

X. Conclusion:

The results of the U.S. studies do not adversely differ significantly from the results of the two pivotal French clinical trials which were the basis for the approvable letter to the sponsor September 18, 1996.

XI. Recommended Phase 4 Studies:

The medical officer, in his revised original NDA review, recommended that phase 4 studies with the following objectives be conducted:

A. To monitor the adequacy of the distribution and credentialing

system.

B. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

C. To assess the long-term effects of multiple use of the regimen.

D. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

E. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

F. To ascertain the effect of the regimen on children born after treatment failure.

The phase 4 recommendations were included in the approvable letter to the sponsor dated September 18, 1999.

XII. Consideration of Advisory Committee Members' Comments:

Part of the review process for this application included seeking expert advice from members of the FDA Reproductive Health Drugs Advisory Committee at a public meeting July 19, 1996. The committee voted 6-0 (with two abstentions) that the pivotal studies (French studies) presented at that time showed that the benefits of a mifepristone and misoprostol regimen for terminating early pregnancies outweighed its risks. The studies presented to the committee involved women treated within 49 days of the beginning of their last menstrual period.

Preliminary safety data from recently completed U.S. trials were also presented.

The committee recommended some phase 4 studies and individual committee members offered some individual comments for consideration by the FDA staff, particularly comments regarding labeling and the drug distribution system. All comments were carefully and fully considered and, to the extent possible, implemented.

The applicant was asked September 18, 1996 to submit a comprehensive description of the proposed distribution system. The following complete response from the applicant was submitted to FDA August 18, 1999 regarding the distribution system:

"The details of the distribution system for the product are in the process of being worked out with the proposed distributor. However, the following key principles will be adhered to in the final distribution arrangements:

- Product will only be available from one or two distributors nationwide and not through retail pharmacies or direct to physicians from the manufacturer.

- Each physician interested in obtaining the product must request the product from the distributors, register with them and open an account.

- Access to the distributors will be through the distributors' general order system and through a specially established toll free telephone number with product ordering as an option.

- Aside from standard credit checks run by the distributors to open a new account, each requesting physician will be required to register by providing their BNDD # and their state Medical License #, and signing a letter that they have the following:

  - The ability to accurately confirm the duration of pregnancy

  - The ability to determine blood Rh factor

  - Access to medical facilities equipped to provide emergency care should that become necessary.

In this same letter they will also be asked to indicate their agreement to:

- Obtain signed acknowledgment from the patient that they have been provided with the product label, that they have read and understood the patient information, have had the procedure, its risks and benefits explained to them, and that they agree to follow the treatment procedure.

- Place the dose # on the acknowlegement and in the patient record.

- Maintain complete records for each patient including blood tests, ultrasound examinations and progress noted.

- Fill out and return AE (Adverse Event) cards to the distributor, identifying patient by dose # only.

- Use every effort to ensure patients return for their follow up visit 14-20 days after taking the product.

- Provide the distributor with as much information as possible if there is an ongoing pregnancy following completion of the treatment procedure and this pregnancy is not terminated.

In addition, the toll free telephone number will enable providers to request training materials and information, and speak to an experienced medical consultant about either a non-emergency patient issue or an urgent medical problem or possible complication. Through a separate routing on the toll free telephone number, patients will have access to general information about the product, a provider location near them and web page addresses for more information.

The final distribution system will be more fully developed in the next few months but will always attempt to insure that the drug is only supplied to qualified physician/hospitals who register with the distributor, that the patient is given access to the product label and that the product # is placed on the acknowledgment in the patient's file and that the anonymity of the patient is maintained.

Market launch will not occur until the distribution system is finalized and there are adequate systems in place to track shipment and use."

FDA requested six phase 4 studies of the applicant's August 22, 1996 (and reminded them of their commitment to perform them in the approvable letter dated September 18, 1996). The requested studies are listed below:

1. To monitor the adequacy of the distribution and credentialing system.

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

6. To ascertain the effect of the regimen on children born after treatment failure.

The applicant's complete response was submitted to FDA August 18, 1999 regarding the requested phase 4 studies as follows:
"We are mindful of our Phase 4 commitments as outlined in the Population Council's letter to FDA dated September 16, 1996. We plan to discuss in more detail and develop a consensus with the FDA post-NDA approval.

1. The Council recognizes the need for additional information about our proposed distribution and credentialing system and the necessity for making certain that it is designed to result in safe and efficacious abortions for women and in properly controlled access to the product. We will provide the FDA with a detailed product distribution and provider credentialing plan that describes our own monitoring indicators, and we would welcome additional discussion with the Agency at that time. We intend to monitor the distribution and credentialing system but we do not believe that the frequency of post-surgical complications will necessarily be a meaningful indicator of its effectiveness.

2. Although the Council cannot commit to a study that follows all women who have surgical abortions following failed mifepristone abortion, we would propose to investigate treatment failures among a representative sample of providers for a mutually agreeable period of time, for instance six months or one year. In such an investigation, we would classify women undergoing medical abortion according to whether they 1) completed their abortions successfully; 2) had a failed medical abortion and required a surgical abortion; 3) required surgical intervention for other reasons; or 4) were lost to follow-up.

   We are not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing this, as it could violate women's privacy.

3. A prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades. However, the Council has been informed that central registries of mifeprostone users exist in Europe. We will examine these data sources to determine what can be learned about multiple use. In addition, in future studies of the regimen carried out by the Council in the U.S., we will attempt to develop a cohort of women who report more than one use of the regimen and agree to be followed.

4. We are willing to supply treatment failure data from a sample of providers for a mutually agreeable period to time, for instance six months or one

year, bearing in mind that such data will not include women lost to follow-up.

5. The Council agrees that it is desirable to have additional information on users of the regimen who are under age 18, or over age 35 or who are smokers. From the French and United States clinical trials, we do have some data on women who were more than 35 years old and on women who smoked. The French trials also included some subjects who were under age 18 years of age. We will submit an analysis of our safety and efficacy data on these subgroups. In addition, data on women under 18 or over 35 years of age and those who smoke will be collected in the sample of women we have agreed to study, as described in item Number 2 and 4 above.

6. Since live births are extraordinarily rare as outcomes of treatment with mifepristone (e.g. approximately 19 out of more than 250,000 in the French database) this issue is best approached by reporting through providers who utilize the regimen. We will instruct our distributor to include materials for providers that ask them to report to the distributor any treatment failure in which the woman decides to continue her pregnancy. The provider will ascertain which of these women agree to be followed to document the health of any children born of such pregnancies. In addition, any spontaneous reports of live births of children exposed to mifepristone *in utero* will be investigated."

Other issues raised by individual advisory committee members are addressed below:

While the DOSAGE AND ADMINISTRATION section of the labeling states that mifepristone may be administered by or under the supervision of a physician trained in abortion, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies, and with access to emergency medical facilities, the applicant has not mentioned anything about conducting training seminars for use of mifepristone, without financial incentive to physicians, and distributing the drug only to those physicians who completed the training. Perhaps the applicant will address this point when the details of the distribution system are submitted to FDA.

The applicant should be able to assess compliance with return visits of patients in the phase 4 studies to be performed.

A surgical termination, if needed, should be provided at no additional cost to the patient. It should be part of the mifepristone-misoprostol method of abortion.

Reasonable attempts to contact patients who do not return to confirm the abortion should be made by the physician.

The applicant intends to monitor the distribution system to ensure that only qualified physicians are treating patients.

The applicant will monitor the number of failed medical terminations and any resulting surgical complication.

The applicant will examine central registries of mifepristone users in Europe to determine what can be learned about multiple use. In addition, the applicant proposes to attempt to develop a cohort of women in future studies in the United States who report more than one use of the regimen and agree to be followed.

The applicant has some data on women who were more than 35 years of age, on women who smoked, and on women under 18 years of age. They will submit an analysis of safety and efficacy data on these subgroups. In addition, data on these subgroups will be collected during the phase 4 studies.

The outcomes of pregnancies not terminated by medical or surgical abortion should be followed up and reported by the physician. This should be part of the credentialing and distribution system.

Conditions of exclusions in the clinical trials are in the labeling.

There is no age restriction in the labeling. Women under 18 years of age or over 35 years of age were arbitrarily excluded from the clinical trials, but there is no biologic reason to think that the efficacy and safety of drug administration to these age groups is any different from that of women 18-35 years of age.

The labeling states that misoprostol should be taken two days after ingesting mifepristone.

Women who smoked at least 10 cigarettes per day were excluded from the French studies. Women in the French studies were informed that they should neither smoke nor drink alcohol during the 48 hours following mifepristone administration and on the day misoprostol was to be administered.

Women in the U.S. studies were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Women were excluded from the U.S.

studies if they were over 35 years of age, smoked more than 10 cigarettes per day, and had another risk factor for cardiovascular disease. The labeling contains a cautionary statement that women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone. The labeling does not contain a statement that alcohol and/or tobacco should be avoided during treatment. Myocardial infarction has been associated with the administration of an intramuscularly administered prostaglandin, sulprostone, but no such association has been reported with the administration of misoprostol. The labeling for misoprostol does not contain any statement regarding avoiding smoking.

Several comments regarding labeling were made by individual advisory committee members and have been throughly considered.

Overall, I do not think that the labeling imparts an impression to the physician or patient that the treatment regimen is "free of adverse effects and free of actually serious side effects."

The use of mifepristone and misoprostol extends the options available to women for the elective termination of early pregnancy, but it is inappropriate to directly compare this regimen with surgical termination in terms of adverse events. For example, bleeding and cramping are to be expected with mifepristone and misoprostol and not generally expected with surgical termination. The two methods are usually appropriate for abortion at different gestational ages. Medical abortions are done usually during the fifth to seventh weeks of gestation. Surgical terminations are usually not done before the sixth week of gestation.

Reference to drugs known to cause enzyme induction has been deleted.

The risk of malformation occurring if pregnancy is not terminated after drug administration appears in table 2 of the labeling.

The labeling states that a surgical termination must be recommended for patients who have an ongoing pregnancy because of the risk of fetal malformation resulting from the treatment procedure.

The physician labeling mentions that although specific drug interactions have not been studied, it is possible that interactions could occur with drugs like aspirin or other non-steroidal anti-inflammatory agents that modify or inhibit prostaglandin synthesis and metabolism. The only available study, however, found no evidence that non-steroidal antinflamatory drugs inhibit the ability of misoprostol to induce uterine

contractions and expulsions. In the patient labeling, the patient is instructed to advise her medical provider of all the medications she is taking and not to take any of them or any other medications during the treatment procedure without first telling her medical provider.

The mifepristone labeling states that since the effects of mifepristone on infants are unknown, and it is not known if misoprostol or its active metabolite is excreted in human milk, breast feeding women should consult with their medical provider to decide if they should discard their breastmilk for a few days following administration of the medications.

The labeling for misoprostol states that it is not known if the active metabolite (misoprostol acid) is excreted in human milk, and therefore, misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Two days is the optimal time to administer misoprostol after the administration of mifepristone because mifepristone requires 36-48 hours to sensitize the uterine muscle to prostaglandins. This information could be added to the labeling.

We do not know if, or to what extent, effectiveness decreases if administration of misoprostol is delayed past two days after the administration of mifepristone. We do know that administration of misoprostol 36-48 hours after the administration of mifepristone is well founded, based on the mechanism of action. The labeling does state that misoprostol should be administered two days after administration of the mifepristone.

Most of the data available are from women 18 years of age or older. However, the drug regimen is expected to be as safe and effective for pregnant women under the age of 18 years as it is for those over the age of 18 years.

Consideration should be given to including a statement under PRECAUTIONS in the physician labeling that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies of greater than 49 days.

Consideration should also be given to including a statement in the patient labeling under "Are there any reasons that I should not have the treatment procedure?" that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies greater than 49 days. This could follow the statements in the patient labeling that state,

"You should not have the treatment procedure if your medical provider determines that the duration of your pregnancy is more than 49 days. For many women this means that the first day of your last period was more than 49 days ago."

The physician labeling contains a PATIENT INFORMATION section that includes the statement, "Before giving you any medication, your medical provider will ask you to sign a statement that you have decided to terminate your pregnancy, and that you have read and understood this information." An ACKNOWLEGEMENT is included in the PATIENT INFORMATION section for the patient and medical provider to sign. Consideration should be given to adding the statement, "My medical provider has confirmed that I am pregnant and that the pregnancy is not greater than 49 days" and a statement that, " My medical provider has discussed with me alternatives to medical abortion including surgical abortion and continuation of this pregnancy."

Everyone who was a member of the advisory committee when mifepristone was presented and who is still a special government employee was sent the results of the U.S. studies in the form of a copy of the article, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States" by members of the Population Council published in the April 30, 1998 issue of the New England Journal of Medicine. The article accurately and succinctly summarizes the results of the studies.

XIII. Recommendation:

Approval of this application is recommended provided that the labeling is satisfactorily revised and the complete details of the distribution system which are yet to be submitted are acceptable.

/S/

/S/ 1/27/00

APPEARS THIS WAY
ON ORIGINAL

SEP 13 2000

September 12, 2000

Mifepristone Tablets, 200mg
NDA 20-687

Population Council
Safety Update Report #3

Medical Officer's Review of Safety Update No. 3 Dated March 31, 2000

This NDA Safety Update Report summarizes the body of information which has been obtained by the Population Council since the cut-off date for the previous NDA Safety Update Report submitted August 3, 1999. The primary source of new information for this report is the Periodic Safety Update Report #9 prepared by the manufacturer of mifepristone, as well as from foreign clinical studies sponsored by the Population Council and from the literature. The cut-off date for this third report is February 29, 2000.

The report from presents information from investigational and marketing experience with the product received by that company from worldwide sources. As stated in that report, there have been no specific actions taken with respect to the product for safety reasons such as rejection, withdrawal or suspension of marketing authorization, restrictions to distribution, suspension of clinical trials, modifications of dosage formulation, or changes in target population or indications. It is stated that in connection with new product approvals by European Union member countries via the mutual recognition procedure, some new textual changes were made to product labeling to reflect common usage practice and for purposes of accuracy and explanation.

One new area of safety concern is apparent in the new information presented in this NDA Safety Update Report. Following queries concerning the use of mifepristone in patients with acute hereditary hepatic porphyrias, conducted an experiment at The chick embryo liver in ovo is a validated model system and currently used to identify "inducing" effects of drugs by measuring increases in hepatic delta amino levulinate synthetase, a rate controlling enzyme, resulting in overproduction of porphyrin and cytochrome P 450. Mifepristone crystalline powder was tested on that model and appeared to be highly toxic on the chick embryo liver. Therefore, concluded that the drug should be contraindicated in patients with inherited porphyrias. This contraindication has been added to the updated Master Data Sheet dated December 1999 by It should be considered for inclusion in the labeling for Mifeprex as a contraindication, but since the contraindication would be based upon the results of a single nonclinical safety study, I am of the opinion that it does not warrant being in the labeling unless further confirmatory data becomes available.

The known number of subjects exposed to mifepristone in clinical studies for various indications is 32,439. Over patients have received mifepristone in commercial distribution since its initial marketing in France in 1989. No clinical studies were conducted in the U.S. by the Population Council during the period covered by this NDA

Safety Update Report.

Protocol 171 (not conducted under an IND) has recently been completed in India for pregnancy termination in 900 women. There were no hospitalizations and no unexpected adverse events. Losses to follow-up were 3.5% and 4.4%.

Protocol [redacted] not conducted under an IND) is ongoing [redacted]

Records have been maintained by [redacted] of ongoing pregnancies following administration of mifepristone and a prostoglandin for medical termination of the pregnancies. There are now reports of 107 ongoing pregnancies. Nine cases of fetal abnormalities have been reported as having occurred in association with these pregnancies. Eight of these occurred with the use of mifepristone and gemeprost. One occurred with the use of mifepristone alone.

Mifepristone is now approved for marketing in 21 countries.

The information contained in this Safety Update Report is consistent with the cumulative experience gained to date on mifepristone and does not reveal any unexpected, unanticipated safety issues that would change the benefit to risk ratio.

[redacted] /S/

JAN 27 2000

NDA 20-687
Population Council

Mifepristone 200 mg Oral Tablets
Review completed November 19, 1999

Medical Officer's Review of Safety Update Report No. 2 Dated August 3, 1999

This second NDA Safety Update Report includes accumulated information relative to the safety of mifepristone which has been obtained by the Population Council since Many 25, 1996, the cut-off date for the first Safety Update Report submitted on June 20, 1996. The cut-off for this second report is June 30, 1999.

Information in the report includes that obtained from recently completed and ongoing clinical trials with the product sponsored by the Population Council and by the manufacturers, Roussel Uclaf Additionally, the report contains Periodic Safety Update Reports prepared by the French manufacturers to summarize the worldwide safety experience with the product, updated information on international regulatory approvals and new information obtained from the literature. The report also contains a Clinical Expert Report on mifepristone which was prepared by and which summarizes the accumulated clinical documentation on the efficacy and safety of the product.

Five periodic safety update reports are submitted covering the period December 1, 1995 - August 31, 1998. An estimated patients received mifepristone under marketing conditions during this period.

In addition to the periodic safety update reports, international reports of adverse reactions have been submitted in two other formats: 1) two quarterly safety line listings of safety reports from clinical trials and of the drug during the period of April 1, 1996 - September 30, 1996 when Roussel Uclaf was responsible for the drug and 2) five individual safety reports (and one follow-up report) received form Roussel Uclaf that were reported to IND

The periodic safety update reports provide a comprehensive summary of the safety information received by Roussel Uclaf from worldwide sources during the covered time periods. Three of the five individual safety reports are also included in the periodic safety update reports. A total of 67 reports were received during a 32 month period when patients received mifepristone. This is one report per patients treated. A total of 28 of these adverse events were assessed as serious. This is one serious report per patients treated. Five of these adverse events were some sort of urticaria or allergic reaction. One instance of disseminated intravascular coagulation was reported from the United Kingdom. Five

of the reports were of fetal abnormalities. The other reports were diverse. No unexpected safety issues are raised by this safety update report. Overall safety results are similar to those seen in the pivotal French studies and in the U.S. studies.

In the period since 1987, Roussel Uclaf have received information on continuing pregnancies after administration of mifepristone or mifepristone and prostaglandins for medical termination of the pregnancies. A report, updated through June 1999, includes 87 reports of ongoing pregnancies, of which 26 followed the use of mifepristone alone and the remainder followed the use of mifepristone and a prostaglandin (or unknown). Nine reports of fetal anomalies have been received. Mifepristone alone was used in one report and mifepristone and gemeprost was used in eight reports. The one report of a fetal anomaly in a patient who received mifepristone alone resulted in a therapeutic termination of pregnancy with cleft palate and sirenomelia which was believed not to be drug related because of embryogenesis considerations. Of the nine reports of fetal anomalies, three occurred in babies at term. One had bilateral talipes (club foot), one had fingernail defect 3, and the third had a heart malformation. Fifteen of the 87 ongoing pregnancies were lost to followup.

A total of 33 normal babies have been born to women who received mifepristone alone (10), mifepristone plus misoprostol (11), or mifepristone plus some other prostaglandin (12). Data are too limited to determine whether mifepristone is a human teratogen.

Ninety articles published between 1996 and 1999 are submitted. These studies report the use of mifepristone in different clinical conditions, variable dosages, and for variable time durations. There is nothing reported in any of these articles that would change the safety profile of mifepristone for early abortion.

In the reports of early pregnancy termination, adverse events and efficacy reported are similar to that reported in the pivotal French studies and in the U.S. studies.

Unrelated to pregnancy termination, but of interest, are two reports where mild elevations in hepatic transaminases were noted in some subjects. Kettel reported 7 subjects with endometriosis treated with mifeprisone, 5 mg daily for six months. Subjects with liver function abnormalities were excluded from treatment. One of the 7 subjects experienced a mild increase in liver transaminases. Perrault reported 28 subjects with untreated metastatic breast carcinoma treated with mifepristone, 200 mg daily. Mild elevations of AST were reported in 6 of the 28 subjects. (Six subjects had metastatic liver disease. It is not known how many, if any, of these subjects with metastatic liver disease were among the six reports of elevated AST.) These mild elevations in hepatic transaminases are of interest because some such changes were noted very early in abortion dose finding studies. However, 248 subjects in the U.S. studies had a full panel of laboratory tests at baseline and at visit 3 including alkaline phosphatase, AST, ALT, and LDH. The median changes noted were small and not of clinical significance.

The Clinical Expert Report on Mifepristone in Termination of Pregnancy is a review of the clinical documentation forming the basis for approval, key results from the published trials, and post-marketing surveillance data. It contains no new information.

We are informed that mifepristone was approved in eight countries (including Germany) July 6, 1999 under the mutual recognition procedure of the European Union.

No new areas of safety concern are apparent. Information contained in this safety update report is consistent with the cumulative experience gained to date from the pivotal French studies and the U.S. studies. The risk-benefit assessment remains unchanged.

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APPEARS THIS WAY
ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 28, 1996

Medical Officer's Summary of Safety Update Dated
June 20, 1996

Included in the Safety Update Report received June 27, 1996 are two new clinical study reports as well as new information regarding study reports previously submitted.

The first new clinical study report is entitled, "The Efficacy and Safety of Mifepristone 600 mg in a Single Dose in Combination with Intravenously Administered Sulprostone (Nalador) in Therapeutic Termination of Second Trimester Pregnancy". The second new clinical report is entitled "Role of Cortisol in the Thermal Response to Alimentation: Effect of Mifepristone" and consisted of twelve healthy, male volunteers, six of whom received a single 600 mg tablet and six of whom received a placebo.

Neither of the two new clinical study reports reveal any additional safety concerns not identified in the two pivotal clinical studies.

Newly completed clinical trials include three studies of labor induction, two studies of breast cancer, and the United States clinical trials of early pregnancy termination. Laboratory data from these completed studies have not yet been analyzed and, therefore, no information on laboratory data are reported in this safety update. Final data analysis and study reports for these six studies have not been completed. The results for termination of pregnancy studies conducted in the United States are expected to be in full agreement with the two pivotal clinical studies. No unanticipated safety issues were raised in these studies. Preliminary examination of information from the United States studies as it was forwarded weekly from the clinics directly to the sponsor during the course of the trials indicates that the final, analyzed results will be similar to those obtained in similar clinical trials of the same medical regimen.

The literature update includes eleven articles published in 1995 and one article published in 1996. Three articles are of particular interest. One is the publication of one of the pivotal clinical studies (FF/92/486/24) by Aubeny et.al. The second is entitled "A Comparative Analysis of Fall in Hemoglobin Following Abortions Conducted By Mifepristone (600 mg) and Vacuum Aspiration" by Thonneau et. Al. The investigators found significant blood loss in the two weeks following abortions by the mifepristone/sulprostone protocol while hemoglobin concentrations remained stable in women who had vacuum aspiration. Women who took mifepristone experienced a mean fall of 0.7 g/dl in hemoglobin two weeks after the abortion. The third article entitled "Clinical, Hormonal, and Sonographic Predictors of Successful RU-486-Induced Abortions" was by Menashe et.al. A small hematoma, seen as a localized detachment of the gestational sac, was observed in the decidua capsularis in women who aborted successfully. A significant decrease in plasma levels of estradiol and progesterone and significantly increased cortisol levels in the plasma of the patients who aborted were observed by the seventh day following treatment.

Table four of the Safety Update Report contains adverse reactions from all sources reported to Roussel Uclaf which were summarized in the quarterly line listings covering July 1, 1995 to September 30, 1995; October 1, 1995 to December 31, 1995; January 1, 1996 to March 31, 1996 and reported in the Periodic Safety Update No. 3 dated January 1996 for the period June 1, 1995 to November 30, 1995.

Of a total of forty eight patient reports of adverse experiences listed in Table 4, twenty-eight were reported from patients enrolled in the United States studies (protocols 166A and B). Of these twenty-eight reports, nineteen were metrorrhagia, three were abdominal pain, two were dehydration, and there were one each of depression, viral meningitis, vomiting, and syncope. Vacuum aspiration or D&C was performed in twelve cases of metrorrhagia and a blood transfusion was given in one case of metrorrhagia. Concomitant hypotension was also reported in four patients with severe metrorrhagia. The patient with syncope presented with a marked vasovagal reaction fifteen minutes after misoprostol administration.

In the section of the Safety Update Report entitled "Tolerance of RU 486 During United States Studies" there is Table 1 which was submitted to the sponsor by Russell Uclaf June 7,1995 which indicates that there were forty-seven serious adverse events plus 8 non serious adverse events in the United States studies (protocols 166 A and B). Table 2 indicates that of the forty-seven serious adverse events forty-one were related to bleeding, two to hypotension, and one each to vomiting, chest pain, infection, and accidental injury.

[redacted]

Also included is a half page document entitled "Notifications Report to Roussel Uclaf from Study English PMS" which lists seven reactions occurring in five patients. There were three reports of uterine hemorrhage, one incomplete abortion with bleeding, one convulsion, one congenital nail disorder, and one report of lack of efficacy.

Also included is a section entitled "New Foreign Marketing Information" which consists only of a core product information document from the product manufacturer revised in March 1995.

Since the start of the use of mifepristone until November 30, 1995, Roussel Uclaf has recorded fifty-three cases of continued pregnancy after the intake of mifepristone for early pregnancy termination (alone or associated with a postaglandin analog).

Among these fifty-three cases:

Nineteen pregnancies were delivered at term (or close to it):
Fifteen were uneventful pregnancies with children normal at birth.
One was normal but born prematurely (33-34 weeks) from caesarean section
One was normal except for common slight bilateral talipes.
One case involves unilateral fingernail defects.
One child was reported as strictly normal at birth but it was known that when she was three months old, the infant was diagnosed as having an autoimmune disorder with chronic giant cell hepatitis and immunohemolytic anemia and later died of severe infectious pneumonia likely exacerbated by immuno-suppressive drugs. The reporting physician's opinion (an expert in teratogenicity) was that the onset of the autoimmune disorder was coincidental and that the role of mifepristone could be reasonably excluded.

In fifteen cases information on further condition of the fetus was made available, mainly in the cases where pregnancy is known to have been terminated later:

In nine cases, termination was performed voluntarily and information either from histologic examination or from ultrasound was that the fetus was normal.

In one case, at therapeutic termination the fetus was noted to have sirenomelia associated with other fetal malformations. The opinion of the consulting embryologists to whom the case was submitted by Roussel Uclaf was that the role of mifepristone was very unlikely. This case has been published (Pons J.C. and all : Lancet, 1991, 328: 763).

In five cases of ongoing pregnancy, the latest available information during second trimester examination indicated normal pregnancy and fetus development.

In six cases, no information on the fetus could be obtained but pregnancy was known to have been terminated later.

In thirteen cases, no further information was made available; in most cases patients were lost to follow-up, and in some cases pregnancy is still ongoing.

Comment: This Safety Update does not reveal any unexpected, unanticipated safety issues that were not made known in the original submission of the NDA.

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Concur: /S/ 9/11/96

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 29, 1996

Medical Officer's Review of Safety Update Including a Summary Of International Post-Marketing Surveillance Data Dated July 25, 1996.

Submission dated July 25, 1996 contains summaries of all the safety information available to the sponsor from Roussel Uclaf International (France, Sweden, United Kingdom) post-marketing surveillance reports, starting from 1989, the first year mifepristone was on the market in France.

Spontaneous notification of suspected adverse events reported in post-marketing surveillance of mifepristone from June 1989 to June 1995 are listed in Table 7 of the submission. Causality by mifepristone is judged to be "unlikely", "unrelated", "not assessable", "insufficient data", "misuse", or "rumor" in the vast majority of cases. Adverse events that were possibly or probably related to drug use were usually expected events such as metrorrhagia. The most commonly used prostaglandin analogue during this period was sulprostone, given by injection.

The Mifepristone Safety Report covering the period January 1, 1991 through December 31, 1992 covers the first eighteen months since the launching of mifepristone in the United Kingdom. It also includes the period of discontinuation of sulprostone and the introduction in France of misoprostol as a possible alternative prostaglandin analogue. The report also contains the entire safety information available since [redacted] early pregnancy termination. In July, 1992, two new indications of mifepristone were approved in France, "therapeutic termination of second trimester pregnancy" and "labor induction in utero fetal death". [redacted]

The International Safety Report Periodic Update from January 1, 1993 to May 31, 1995 contains no unexpected or unanticipated reports of adverse reactions that were not already known. There were no post-marketing phase IV or surveillance studies reported in final form during this period. There is mention of about three thousand four hundred and thirty-five patients enrolled in the post-marketing surveillance program conducted by Roussel Uclaf in the United Kingdom during the period of this report, but no additional information is available.

Periodic Safety Update Report No. 3 from June 1, 1995 to November 30, 1995 has been reviewed previously by the Food And Drug Administration Medical Officer and his comments are in his Safety Update Review dated August 28, 1996. No unexpected or unanticipated adverse reactions were found in this periodic report.

Comment: From the cumulative experience to date, no new special areas of concern have been identified. The assessment of the risk-benefit ratio of mifepristone is unaltered by the data included in this Safety Update Report.

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Concur: /S/ 9/9/96

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 29,1996

Medical Officer's Review of United States Safety Data Dated July 14, 1996

Submission dated July 14, 1996 is a summary report of the serious adverse events from Protocols 166 A and B during the United States clinical trials. All of these reports have been submitted previously in IND

A total of fifty-two subjects had at least one SAE. There was more than one adverse event reported for most subjects. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least four subjects are listed in the summary below.

Total No. of Patients	Total No. of Clinics	Total No. of Adverse Events	Total Number of Treatments				Total No. Hospitalized
			D&C/ Asp.	Meth./ oxy.	IV Fluids	Transfusion	
52	13	Hemorrhage 41 Faint/Dizziness 20 Cramping 14 Vomiting 06 Hypotension 05 Tachycardia 04	34	15	28	04	26

These serious adverse events resulted in the hospitalization of twenty-six subjects. Four subjects received transfusions. A total of twenty-eight subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of thirty-four subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen subjects recieved methergine or oxytocin for treatment of bleeding, although eleven of these subjects eventually had a surgical procedure.

It is not possible to make a complete comparison of the serious adverse events reported in the United States trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the United States trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, t this time comparisons between the United States and NDA pivotal studies can only be made with the serious adverse events

reported from these fifty-two United States subjects, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire United States database. However, some general comparisons can be made. The total number of subjects enrolled in United States Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the United States trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metrorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by forty-one subjects in the United States studies. In the NDA pivotal studies, fifty-two subjects reported metrorrhagia or excessive bleeding, which was categorized as severe in twenty-one subjects. However, the manner in which the bleeding was treated differed in the two studies. In the Unites States trials, thirty-two of the thirty-four surgical interventions (D&C or aspiration) were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of fifteen subjects received surgical interventions for bleeding. The greater number of surgical interventions by United States investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the United States, but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The United States investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were five cases of hypotension, in the United States trials, although blood pressure readings were given for only two of these subjects. There were seven cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia for United States subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported in the United States subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the United states database.

Conclusion:

The SAEs reported during the United States trial do not appear to differ significantly from those reported in the pivotal NDA trails, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the United States trials may be explained by the initial inexperience of United States clinicians in providing medical abortion. Investigators in the United States trials have indicated that there was a learning curve associated with the treatment of bleeding during the trial. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies.

In summary, the current comparison of SAEs between the United States trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of United States settings.

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Concur: /S/ 9/9/96