Exhibit I

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

(b) (6) provided recommendations to (b) (6) based on its review of the proposed modifications to the REMS. In the (b) (6) review dated March 29, 2016, the primary reviewer, (b) (6) indicated (b) (6) agreement with the following Applicant-proposed changes:

- Removal of the term "under Federal law" from the Prescriber's Agreement
- Replacement of the word "physician" with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex; (b) (6) believes that the Applicant's proposed terminology of " (b) (4) is too broad and that a more appropriate description is "healthcare provider who prescribes."

In the course of this review, input was obtained from the (b) (6) and (b) (6) and (b) (6) considered the recent REMS Assessment data submitted by the Applicant in June 2015, postmarketing summary reporting by the (b) (6) (b) (6) safety data obtained over the past 16 years, and information about current clinical practice. Based on the information reviewed, as well as current FDA thinking about REMS language and organization, (b) (6) and (b) (6) considered the ongoing need for each REMS element to ensure that the benefits outweighed the risks of Mifeprex and proposed additional modifications to the REMS, including:

- Removal of the Medication Guide from the REMS. While the Medication Guide remains an important tool for patient education, and will still be distributed to each patient as part of labeling, it is not a necessary element of the REMS to ensure that the benefits outweighed the risks of Mifeprex
- Modification of Element to Assure Safe Use (ETASU) A, i.e., the Prescriber's Agreement. (b) (6) recommends changing the name of the document to the Prescriber's Agreement Form to be consistent with terminology used in other REMS programs. The gestational age at which Mifeprex may be used should be modified in accord with revised labeling in the Prescribing Information. References to "physician" should be changed to "healthcare provider who prescribes."
- Modification of ETASU D, i.e., the Patient's Agreement. (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
    - The established safety profile over 15 years of experience with Mifeprex is well-characterized and known serious risks occur rarely
    - The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208

- 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 (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

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[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 endi
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 medi 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*	Total: 92.9%	Serious AEs r discussed
						GA	*≤ 49: 96.3%* *50-56: 86.5%* *57-63: 96.3%*	
Chai 2013 Hong Kong	DB RCT	90 (45 in each arm)	63 days			Regimen: Buccal vs. SL miso	Buccal: 95.4% SL: 97.8% NS different Both ROAs had 100% success in GA ≤ 49 days	AEs similar 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	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*	
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 s 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 63 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 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 mis 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: 10.9% 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% Buccal vs ora ↓nausea, diar
						Dose interval	*24 hr: 94.2%* *24-48 hr: 96.8%*	

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 c 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 o 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+: 9.1%
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 bleedi 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.