Common Drug Review
Clinical Review Report

May 2017

Drug	Mifepristone and misoprostol (Mifegymiso)
Indication	For medical termination of a developing intrauterine pregnancy with a gestational age up to 49 days as measured from the first day of the last menstrual period (LMP) in a presumed 28-day cycle.
Listing request	Not specified
Dosage form(s)	200 mg oral tablet and 200 mcg oral tablet
NOC Date	July 29, 2015
Manufacturer	Celopharma Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in obstetrics and gynecology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

CDR	CADTH Common Drug Review
CI	confidence interval
CIHI	Canadian Institute for Health Information
D&C	dilation and curettage
HRQoL	health-related quality of life
ITT	intention to treat
IV	intravenous
LMP	last menstrual period
PP	per protocol
ROA	route of administration
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SL	sublingual
SOGC	Society of Obstetricians and Gynaecologists of Canada
TEAE	treatment-emergent adverse event
WHO	World Health Organization

EXECUTIVE SUMMARY

Introduction

Medical abortion is the process by which a pregnancy is voluntarily terminated through the administration of one or more medications.[1] In Canada, the primary method for abortion is surgical, mainly because of the lack of an approved medical intervention.[1] The choice of abortion method is dependent upon availability, gestational age, and patient preference.[2] Based on data reported to the Canadian Institute for Health Information, there were 81,897 induced abortions performed in a Canadian hospital or clinic setting in 2014.[3]

The 2016 clinical practice guideline of the Society of Obstetricians and Gynaecologists of Canada on medical abortion for first-trimester pregnancies recommends oral mifepristone 200 mg and misoprostol 800 mcg via the buccal, vaginal, or sublingual (SL) routes as the regimen of choice for medical abortion up to 70 days' gestation in eligible women.[1] Alternative evidence-based medical-abortion regimens include mifepristone and misoprostol regimens at higher gestational age (although associated with decreased completion rates) and methotrexate and misoprostol regimens or misoprostol alone for pregnancies up to 63 days' gestation in women with contraindications to mifepristone or methotrexate, respectively.[1]

Mifegymiso is a new combination product containing one 200 mg mifepristone tablet for oral administration and four 200 mcg misoprostol tablets for buccal administration. Mifepristone is a synthetic progesterone receptor antagonist, whereas misoprostol is a synthetic analogue of prostaglandin E1.[4] The recommended dosage of Mifegymiso is 200 mg of mifepristone taken orally under supervision of the prescriber, followed by 800 mcg of misoprostol (four 200 mcg tablets) in a single dose by the buccal route 24 to 48 hours (one to two days) later.[4]

Indication under review[a]
For medical termination of a developing intrauterine pregnancy with a gestational age up to 49 days as measured from the first day of the last menstrual period (LMP) in a presumed 28-day cycle
Listing criteria requested by sponsor
Not specified

[a] There are insufficient data in patients less than 15 years old to establish efficacy and safety. Mifegymiso is not indicated in prepubertal or post-menopausal populations.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of a single oral dose of mifepristone 200 mg and a single buccal dose of misoprostol 800 mcg (four 200 mcg tablets) administered in a sequential regimen for the medical termination of a developing intrauterine pregnancy in women of child-bearing age.

Results and Interpretation

Included Studies

Five prospective trials met the selection criteria for inclusion in the systematic review. Three open-label trials were considered pivotal by Health Canada: Study 1 (N = 442), Study 2 (N = 966), and Study 3 (N = 1,000). As well, two double-blind trials were identified from the clinical literature search: Study 4 (N =

90) and Study 5 (N = 441). Three trials (Studies 1, 2, and 4) were randomized, parallel-group comparisons of different routes of administration of misoprostol (i.e., buccal compared with oral, vaginal, and SL, respectively), all following a single oral dose of mifepristone. Study 5 was also a randomized trial comparing oral mifepristone and buccal misoprostol with buccal misoprostol alone. Randomization was not stratified by any variables in any of the trials. Study 3 was a nonrandomized, single-arm trial of the Health Canada–approved mifepristone and misoprostol regimen. All trials enrolled women of child-bearing age (14 years and older) who were voluntarily seeking medical abortion of a pregnancy of gestational age of up to 56 to 63 days since last menstrual period (LMP). In all of the trials, a subpopulation of women with pregnancies of ≤ 49 days' gestation based on LMP (per the Health Canada–approved regimen for Mifegymiso) could be identified. All five trials were published in the peer-reviewed medical literature.[5-10]

Key limitations of the available evidence are the lack of comparison with surgical abortion or methotrexate and misoprostol (which constitute the standard of care for abortion in Canada), uncertainty whether the subgroups reported in the trials were pre-specified, lack of stratification by gestational age, and lack of control or adjustments of secondary outcomes for multiplicity.

Efficacy

Key efficacy outcomes included in the review protocol were pregnancy outcome and health-related quality of life. Other efficacy outcomes were complication rates (e.g., bleeding, infection, pain), psychiatric/psychological morbidity, health care resource utilization, and patient satisfaction. The included trials did not report any outcomes pertaining to health-related quality of life, psychiatric/psychological morbidity, or health care resource utilization.

Across all five trials, success rates (i.e., the proportion of women with complete abortion without surgical intervention at any time) following 200 mg oral mifepristone and 800 mcg buccal misoprostol ranged from 92.9% to 97.3%. In Study 1, there was no statistically significant difference in success rates between buccal (94.9%) and vaginal (93.4%) misoprostol; however, in Study 2 the difference between buccal (96.2%) and oral (91.3%) misoprostol was statistically significant (relative risk 0.95; 95% confidence interval [CI], 0.92 to 0.98; $P < 0.048$). Study 3 was a single-arm trial in which the success rate was reported to be 97.3%. Study 4 reported success rates of 95.6% for buccal and 97.8% for SL misoprostol, which were not statistically significantly different. In Study 5, the success rate following 200 mg oral mifepristone and 800 mcg buccal misoprostol (92.9%) was statistically significantly higher than following 1,600 mcg buccal misoprostol alone (78.0%), resulting in relative risk 0.84 (95% CI, 0.78 to 0.91; $P < 0.001$). No trials that included surgical abortion as a direct comparator were identified. A systematic review that compared medical and surgical abortion (Appendix 5), reported no statistically significant difference in the rate of failure when mifepristone and prostaglandin for medical abortion was compared with vacuum aspiration for surgical abortion (one trial, odds ratio 2.12; 95% CI, 0.37 to 12.06).[11]

As surgical abortion is the primary method of abortion in Canada, the lack of a direct comparison of Mifegymiso with surgical abortion represents an important evidence gap. It is acknowledged that such a direct comparison is methodologically difficult and that, according to the Society of Obstetricians and Gynaecologists of Canada, despite a lack of direct comparative evidence, regimens of mifepristone 200 mg oral and misoprostol 800 mcg by the buccal/vaginal/SL route are considered as effective and safe as surgical abortion before 49 days following the LMP and are highly effective up to 70 days after the LMP.[1] There is also a lack of direct evidence comparing the 200 mg oral mifepristone and 800 mcg buccal misoprostol regimen with methotrexate and misoprostol, which is the current standard of care

for medical abortion in Canada. According to the clinical expert consulted on this review, the use of methotrexate and misoprostol can take up to four weeks to be effective, which is a major disadvantage. The methotrexate and misoprostol regimen is also less effective as gestational age advances, and there is a serious known risk of embryotoxic or teratogenic effects associated with the use of methotrexate.[1,12]

Success rates with 200 mg oral mifepristone and 800 mcg buccal misoprostol in women with pregnancies of gestational age ≤ 49 days were consistent with those in the overall populations in the trials. It is important that gestational age fall within the limits for medical abortion, as effectiveness of medical regimens decreases as gestational age increases, and underestimation of gestational age could result in a woman receiving a treatment that may be inappropriate for medical abortion.[1] The rates of ongoing pregnancies were reported by gestational age in Studies 2 and 5. Although statistical comparisons were not made between gestational age groups in these trials, the proportion of women with ongoing pregnancies appeared to be higher in women with pregnancies of advanced gestational age (e.g., in Study 2, 3.5% of women in the overall study population compared with 7.9% of women with pregnancies of gestational age 57 to 63 days since the LMP in the oral misoprostol group had ongoing pregnancies).

In all five trials, specific data on the actual amount or duration of bleeding or pain were not available. Rather, in Studies 2, 3, and 5, upon study completion, women were questioned regarding the amount of bleeding or pain they experienced relative to their expectations. The proportion of women who rated the amount of bleeding as "less than expected" ranged from 28.9% to 34.0% with the 200 mg oral mifepristone and 800 mcg buccal misoprostol regimen compared with 28.3% (with the 800 mcg oral misoprostol regimen) in Study 2 and with 26.7% (with the 1,600 mcg misoprostol-alone regimen) in Study 5. Those who rated the amount of bleeding as "same as expected" ranged from 35.4% to 43.6% in the 200 mg oral mifepristone and 800 mcg buccal misoprostol arms compared with 44.0% (in the 800 mcg oral misoprostol group) in Study 2 and 30.1% (in the 1,600 mcg misoprostol-alone group) in Study 5. Those who rated the amount of bleeding as "more than expected" ranged from 27.0% to 30.6% with 200 mg oral mifepristone and 800 mcg buccal misoprostol, compared with 26.0% (with 800 mcg oral misoprostol) in Study 2 and 43.2% (with 1,600 mcg misoprostol alone) in Study 5.

Bleeding times in women with gestational age ≤ 49 days in Studies 1 and 2 were reported in the Mifegymiso product monograph.[4] In Study 1, the mean (standard deviation [SD]) days of heavy bleeding was 2.3 (2.3), normal bleeding was 5.1 (2.9), and spotting was 3.5 (2.5). In Study 2, the mean (SD) days of total bleeding time was 10.8 (3.9), whereas heavy bleeding lasted for a mean (SD) of 2.0 (2.1), normal bleeding for 4.3 (2.8), and spotting for 4.6 (3.2). One patient each in Study 1 and Study 3 required a blood transfusion for excessive bleeding.[4] In Study 4, 66.7% (95% CI, 51.1 to 80.0) of women in the buccal misoprostol group and 73.3% (95% CI, 53.1 to 85.4) of women in the SL misoprostol group reported bleeding on day 15. In the systematic review summarized in Appendix 5, the duration of bleeding with mifepristone and prostaglandin for medical abortion was found to be greater than with vacuum aspiration for surgical abortion (mean difference 2.94 days; 95% CI, 2.10 to 3.78).

In Studies 2, 3, and 5, the proportion of women who rated their amount of pain as "less than expected" ranged from 26.3% to 31.9% with 200 mg oral mifepristone and 800 mcg buccal misoprostol compared with 38.6% (with 800 mcg oral misoprostol) in Study 2 and 33.2% (with 1,600 mcg misoprostol alone) in Study 5. Those who rated the amount of pain as "same as expected" ranged from 25.0% to 38.8% (200 mg oral misoprostol and 800 mcg buccal misoprostol) compared with 34.3% (800 mcg oral misoprostol) in Study 2 and 22.6% (1,600 mcg misoprostol alone) in Study 5. Those who rated the amount of pain as "more than expected" ranged from 29.9% to 46.0% (200 mg oral mifepristone and

800 mcg buccal misoprostol) compared with 25.7% (800 mcg oral misoprostol) in Study 2 and 44.2% (1,600 mcg misoprostol alone) in Study 5.

Overall satisfaction with the 200 mg oral mifepristone and 800 mcg buccal misoprostol regimen ranged from 91.1% to 94.4% in the trials that reported this outcome (Studies 1, 2, and 3). Overall satisfaction with misoprostol administered vaginally was 94.8% in Study 1 and with misoprostol administered orally was 92.6% in Study 2.

Harms

Harms outcomes identified in the review protocol were mortality, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable adverse events (e.g., gastrointestinal-related, reproductive system–related, QT prolongation, embryotoxicity). There were no deaths or WDAEs reported in the included trials.

Overall, TEAEs were experienced by the majority of patients in the trials and were consistent with the known effects of prostaglandins (e.g., nausea, vomiting, diarrhea, dizziness, headache, and thermoregulatory symptoms such as fever and chills).[1] The most commonly reported TEAEs were nausea, vomiting, and diarrhea. The proportion of patients with nausea ranged from 34.2% to 75.1% with 200 mg oral mifepristone and 800 mcg buccal misoprostol regimen compared with 62.0% with 800 mcg vaginal misoprostol, 68.5% with 800 mcg oral misoprostol, 60.0% with 800 mcg SL misoprostol, and 50.9% with 1,600 mcg buccal misoprostol alone. The proportion of patients with vomiting ranged from 20.0% to 47.6% with 200 mg oral mifepristone and 800 mcg buccal misoprostol compared with 31.9%, 43.5%, 33.3%, or 39.9% with 800 mcg misoprostol by the vaginal, oral, and SL routes, or 1,600 mcg misoprostol by the buccal route. Diarrhea was reported in 36.1% to 61.2% of patients with 200 mg mifepristone and 800 mcg buccal misoprostol compared with 23.9%, 38.7%, 37.8%, or 83.9% with 800 mcg misoprostol by the vaginal, oral, and SL routes, or with 1,600 mcg buccal misoprostol alone. There were no deaths reported in any of the included trials, and SAEs were reported in only one study (Study 3).

Other Considerations

The manufacturer has advised that a Supplemental New Drug Submission is currently under review by Health Canada to extend the indication for Mifegymiso to gestational age of up to 63 days and to modify the distribution process in Canada.

Conclusions

In five prospective trials, the regimen of 200 mg oral mifepristone followed by 800 mcg buccal misoprostol 24 to 72 hours later was effective at inducing complete abortion without surgical intervention at any time in women of child-bearing age voluntarily seeking medical abortion for pregnancies with gestational age up to 56 to 63 days. Rates of complete abortion with this regimen in women with pregnancies of gestational age ≤ 49 days were consistent with those in the overall study populations in all the trials. The regimen was also shown to be superior to 200 mg oral mifepristone and 800 mcg oral misoprostol and to 1,600 mcg misoprostol alone. In general, most patients were satisfied with the regimen for medical abortion. Rates of complications were low across all trials. There were no deaths or WDAEs reported in any of the included trials, and SAEs were reported in only one trial. While TEAEs were experienced by the majority of the women in the trials, they were consistent with the known effects of prostaglandins (e.g., nausea, vomiting, diarrhea, and thermoregulatory symptoms). In most of the included trials, the proportion of patients reporting TEAEs was similar between treatment arms, with the possible exception of more nausea, vomiting, and fever/chills with SL administration of misoprostol and more diarrhea with misoprostol alone (which was administered at twice the dose used in the other trials). An important limitation is the lack of evidence directly comparing the Mifegymiso regimen with surgical abortion or methotrexate and misoprostol, which constitute the standard of care for abortion in Canada.

TABLE 1: SUMMARY OF RESULTS

Characteristic	Study 1		Study 2		Study 3	Study 4		Study 5	
	Miso 800 mcg Buccal N = 216	Miso 800 mcg Vaginal N = 213	Miso 800 mcg Buccal N = 421	Miso 800 mcg Oral N = 426	Miso 800 mcg Buccal N = 971	Miso 800 mcg Buccal N = 45	Miso 800 mcg Sublingual N = 45	Miso 800 mcg Buccal N = 210	Miso 1,600 mcg Buccal N = 218
Efficacy Results									
Success, n (%)[a,b]	205 (94.9)	199 (93.4)	405 (96.2)	389 (91.3)	945 (97.3)	43 (95.6)	44 (97.8)	195 (92.9)	170 (78.0)
RR (95% CI)	NR		0.95 (0.92 to 0.98)		NA	NR		0.84 (0.78 to 0.91)	
***P* value**	0.51		< 0.048		NA	NR		< 0.001	
Success ≤ 49 days, n (%)[a,c]	NR	NR	132/137 (96.4)	107/113 (94.7)	540/551 (98.0)	22/22 (100.0)	26/26 (100.0)	105/109 (96.3)	95/121 (78.5)
RR (95% CI)	NR	NR	0.93 (0.86 to 1.00)		NA	NR		0.82 (0.74 to 0.90)	
***P* value**	NR	NR	NS		NA	NR		< 0.001	
Failures, n (%)[b]	11 (5.1)	14 (6.6)	16 (3.8)	37 (8.7)	26 (2.7)	0 (0)	1 (2.2)	15 (7.1)	48 (22.0)
RR (95% CI)	NR	NR	2.29 (1.29 to 4.04)		NR	NR		NR	
***P* value**	NR	NR	< 0.048		NR	NR		NR	
Overall satisfaction, n (%)[d]	196/213 (92.0)	199/210 (94.7)	378/415 (91.1)	389/420 (92.6)	915/969 (94.4)	NR	NR	91/209 (43.5)[e] 97/209 (46.4)	71/218 (32.6)[e] 95/218 (43.6)
RR (95% CI)	NR		NR		NA	NR		0.75 (0.59 to 0.96)[e] 0.94 (0.76 to 1.16)	
***P* value**	NS		NS		NA	NR		0.020[e] NS	
Amount of bleeding, n (%)									
Less than expected	NR	NR	120/415 (28.9)	119/420 (28.3)	296/969 (30.5)	NR	NR	70/206 (34.0)	55/206 (26.7)
Same as expected	NR	NR	181/415 (43.6)	185/420 (44.0)	404/969 (41.7)	NR	NR	73/206 (35.4)	62/206 (30.1)
More than expected	NR	NR	124/415 (29.9)	109/420 (26.0)	262/969 (27.0)	NR	NR	63/206 (30.6)	89/206 (43.2)
Amount of pain, n (%)									
Less than expected	NR	NR	123/415 (29.6)	162 /420 (38.6)	255/969 (26.3)	NR	NR	65/204 (31.9)	69/208 (33.2)
Same as expected	NR	NR	161/415 (38.8)		261/969 (26.9)	NR	NR		
More than expected	NR	NR	124/415 (29.9)	144/420 (34.3)	446/969 (46.0)	NR	NR	51/204	47/208

Characteristic	Study 1		Study 2		Study 3	Study 4		Study 5	
	Miso 800 mcg Buccal N = 216	Miso 800 mcg Vaginal N = 213	Miso 800 mcg Buccal N = 421	Miso 800 mcg Oral N = 426	Miso 800 mcg Buccal N = 971	Miso 800 mcg Buccal N = 45	Miso 800 mcg Sublingual N = 45	Miso 800 mcg Buccal N = 210	Miso 1,600 mcg Buccal N = 218
				108/420 (25.7)				(25.0) 88/204 (43.1)	(22.6) 92/208 (44.2)
Harms Results									
Deaths, n (%)	0	0	0	0	0	0	0	0	0
Pts with ≥ 1 AE, n (%)	NR	NR	393/414[f] (94.9)	405/416[f] (97.3)	858/969 (88.5)[f]	NR	NR	NR	NR
Pts with ≥ 1 SAE, n (%)	0	0	NR	NR	11/969 (11.1)[f]	NR	NR	NR	NR
Pts with ≥ 1 WDAE, n (%)	0	0	0	0	0	0	0	0	0

AE = adverse event; CI = confidence interval; Miso = misoprostol; NA = not applicable; NR = not reported; NS = not statistically significant; Pts = patients; RR = relative risk; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Success defined as complete abortion without surgical intervention at any time. For success, a RR < 1 means the event is less likely to occur in the comparator group than the Miso 800 mcg buccal group.

[b] Results are for all patients regardless of gestational age. For failures, a RR > 1 means the event is more likely to occur in the comparator group than the Miso 800 mcg buccal group.

[c] Results are for patients with gestational age ≤ 49 days with the exception of Study 2, which is for 43 to 49 days. (Note: Results reported for ≤ 42 days were 98.7% versus 97.8%; RR 0.99; 95% CI, 0.93; 1.03.)

[d] Results are for patients who provided a response.

[e] Results are for "very satisfied" (upper) and "satisfied" (lower). For overall satisfaction, a RR < 1 means the event is less likely to occur in the comparator group than the Miso 800 mcg buccal group.

[f] Results are for the safety population.

Source: Middleton et al., 2005,[6,13] Winikoff et al., 2008,[7,14] Pena et al., 2014,[7,15] Chai et al., 2013,[8] Blum et al., 2012,[9] Mifegymiso product monograph.[4]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Medical abortion is the process by which a pregnancy is voluntarily terminated through the administration of one or more medications.[1] In Canada, the primary method for abortion is surgical (i.e., uterine dilation/curettage [D&C] and suction aspiration), mainly because of the lack of an approved medical intervention.[1] Both medical and surgical methods are safe and effective for appropriately selected patients, and the choice of method is based upon availability, gestational age (medical abortion is less successful in late first trimester and beyond), and patient preference.[2]

According to data reported to the Canadian Institute for Health Information, there were 81,897 induced abortions performed in a Canadian hospital or clinic setting in 2014.[3] Of these, 33,931 (41%) were performed in hospitals and 47,966 (58%) in clinics; however, these data are incomplete, as the reporting of clinic data is voluntary and abortions that may have been obtained by Canadian women elsewhere (such as in the US) are not captured.[3] Medical abortion presents an opportunity to facilitate the provision of abortion care in settings that are not identified as abortion facilities and to mitigate some of the logistical challenges reported by rural and hospital-based providers.[1]

1.2 Standards of Therapy

Of the total number of induced abortions reported to Canadian Institute for Health Information by Canadian hospitals in 2014, approximately 96% were surgical procedures (or a combination of surgical and medical procedures) whereas 4% were medical procedures alone.[3] In a 2012 survey of Canadian abortion providers, 29.2% (62 of 212 providers) offered medical abortion, with most (84%) using a regimen involving methotrexate and misoprostol.[1] The 2016 clinical practice guideline of the Society of Obstetricians and Gynaecologists of Canada (SOGC) on medical abortion for first-trimester pregnancies recommends oral mifepristone 200 mg and misoprostol 800 mcg via the buccal/vaginal/sublingual (SL) routes as the regimen of choice for medical abortion up to 70 days' gestation among eligible women.[1] The use of mifepristone in combination with misoprostol for the termination of pregnancies up to 70 days' gestation is approved in the US,[16] and the mifepristone and misoprostol regimen is considered to be the gold standard for early medical abortion by the World Health Organization (WHO).[17] Alternative evidence-based medical abortion regimens include mifepristone and misoprostol regimens at higher gestational age (although associated with decreased completion rates) and methotrexate and misoprostol regimens or misoprostol alone for pregnancies up to 63 days' gestation in women with contraindications to mifepristone or methotrexate, respectively.[1]

The decision between medical and surgical abortion requires an understanding of both options and a review of factors that affect method selection.[1] The differentiating features of medical abortion are the avoidance of surgery, longer procedure time (i.e., days or weeks compared with minutes), generally more pain, heavier bleeding, more physician visits for assessment, medication administration and follow-up, medication costs that may be borne by the patient, and increased anonymity, when compared with surgical abortion. [1] There are a number of conditions for which the use of the mifepristone and misoprostol regimen is absolutely or relatively contraindicated (e.g., ectopic pregnancy, chronic adrenal failure, inherited porphyrias, uncontrolled asthma, known hypersensitivity to any of the components, ambivalence, unconfirmed gestational age, IUD, long-term corticosteroid therapy, and hemorrhagic disorders or use of anticoagulant therapy).[1]

1.3 Drug

Mifegymiso is a new combination product containing one 200 mg mifepristone tablet for oral administration and four 200 mcg misoprostol tablets for buccal administration, supplied in different coloured boxes that are packaged together. Mifepristone is a synthetic progesterone receptor antagonist, whereas misoprostol is a synthetic analogue of prostaglandin E1.[4] When mifepristone blocks progesterone receptors, the endometrium can no longer sustain a growing embryo.[4] Without the effect of progesterone, the lining of the uterus breaks down, and bleeding begins.[4] Mifepristone also triggers an increase in prostaglandin levels and dilates the cervix, facilitating abortion.[4] The subsequent use of misoprostol induces contractions of the smooth muscle fibres in the myometrium, relaxation of the uterine cervix, and evacuation of intrauterine contents.[4]

Misoprostol was previously marketed in Canada as Cytotec 100 mcg and 200 mcg tablets, and was indicated for the treatment and prevention of nonsteroidal anti-inflammatory drug–induced gastroduodenal ulcers and the treatment of duodenal ulcers caused by peptic ulcer disease.[18] The market authorization of Cytotec was cancelled in 2005; however, single-entity misoprostol is currently available as various generic drug products and in combination with diclofenac (i.e., Arthrotec and various generic drug products).

The recommended dose of Mifegymiso is 200 mg of mifepristone taken orally under supervision of the prescriber, followed by 800 mcg of misoprostol (four tablets of 200 mcg each) in a single dose by the buccal route 24 to 48 hours (one to two days) later.[4]

Indication under review[a]
For medical termination of a developing intrauterine pregnancy with a gestational age up to 49 days as measured from the first day of the LMP in a presumed 28-day cycle
Listing criteria requested by sponsor
Not specified

LMP = last menstrual period.
[a] There are insufficient data in patients less than 15 years old to establish efficacy and safety. Mifegymiso is not indicated in prepubertal or post-menopausal populations.

Before prescribing Mifegymiso, physicians must do the following:[4]

- Ensure that patients have access to emergency medical care in the 14 days following administration of mifepristone.
- Schedule follow-up seven to 14 days after patients take mifepristone to confirm complete pregnancy termination.
- Exclude ectopic pregnancy and confirm gestational age by ultrasound.
- Counsel each patient on the risks and benefits of Mifegymiso, including bleeding, infection, and incomplete abortion.
- Obtain the patient's written informed consent to take the drug.
- Complete the mandatory Mifegymiso education and registration programs.

TABLE 2: KEY CHARACTERISTICS OF MIFEGYMISO, METHOTREXATE, AND MISOPROSTOL

Mechanism of Action	Mifepristone is a synthetic progesterone receptor antagonist and misoprostol is a synthetic analogue of prostaglandin E1.	Inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid	Synthetic analogue of prostaglandin E1
Indication[a]	For medical termination of a developing intrauterine pregnancy with a gestational age up to 49 days as measured from the first day of the LMP in a presumed 28-day cycle	For the treatment of numerous neoplastic diseases and as a DMARD	For the treatment and prevention of NSAID-induced gastroduodenal ulcers and for the treatment of duodenal ulcers caused by PUD
Route of Administration	Oral (mifepristone) and buccal (misoprostol)	Oral, intramuscular, intrathecal	Oral, buccal, vaginal, SL
Recommended Dose[b]	Mifepristone 200 mg taken orally followed by misoprostol 800 mcg as a single dose by the buccal route taken 24 to 48 hours later for pregnancies up to 49 days	50 mg orally or intramuscularly followed by misoprostol 800 mcg vaginally 3 to 5 days later for pregnancies up to 63 days	800 mcg every 3 to 24 hours intravaginally or sublingually for pregnancies up to 63 days
Serious Side Effects / Safety Issues	Risk of infection and sepsis, risk of bleeding, embryotoxicity	Fetal death, embryotoxicity, abortion, or teratogenic effects	Abortifacient, congenital abnormalities, and fetal death subsequent to misuse as an abortifacient, uterine perforation with misuse for cervical ripening or labour induction
Other	Only Health Canada–approved drug product for medical abortion	Off-label use for medical abortion	Off-label use for medical abortion

DMARD = disease-modifying antirheumatic drug; LMP = last menstrual period; NSAID = nonsteroidal anti-inflammatory drug; PUD = peptic ulcer disease; SL = sublingual; SOGC = Society of Obstetricians and Gynaecologists of Canada.

[a] Health Canada–approved indication.

[b] Recommended dose for medical abortion per the SOGC clinical practice guideline for medical abortion.[1]

Source: Mifegymiso product monograph,[4] methotrexate product monograph,[12] Cytotec product monograph.[18]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of a single oral dose of mifepristone 200 mg and a single buccal dose of misoprostol 800 mcg (four 200 mcg tablets) administered in a sequential regimen for the medical termination of a developing intrauterine pregnancy in women of child-bearing age.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Women of child-bearing age seeking medical termination of intrauterine pregnancy with a gestational age up to 49 days as measured from the first day of the LMP in a presumed 28-day cycle **Subgroups:** Age, weight, gestational age, and gravidity
Intervention	Mifepristone 200 mg orally as a single dose followed by 800 mcg misoprostol (four 200 mcg tablets) as a single dose by the buccal route 24 to 48 hours later
Comparators	Mifepristone/misoprostol by different ROA Methotrexate/misoprostol Misoprostol alone Surgical abortion
Outcomes	**Key efficacy outcomes:** • Pregnancy outcome (e.g., confirmed by ultrasonography and/or beta-hCG levels) • Health-related quality of life **Other efficacy outcomes:** • Complication rates (e.g., bleeding, infection, pain) • Psychiatric/psychological morbidity • Health care resource utilization • Patient satisfaction **Harms outcomes:** Mortality, AEs, SAEs, WDAEs, AEs of special interest (e.g., GI-related, reproductive system–related, QT prolongation, embryotoxicity)
Study Design	Published and unpublished phase III RCTs

AE = adverse events; beta-hCG = beta-human chorionic gonadotropin; GI = gastrointestinal; LMP = last menstrual period; ROA = route of administration; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Mifegymiso, mifepristone, and misoprostol.

Methodological filters were applied to limit retrieval to systematic reviews, health technology assessments, meta-analyses, network meta-analyses, randomized controlled trials, and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 8, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on March 15, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Clinical trials; and Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings from the Literature

A total of five studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and Table 5 and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

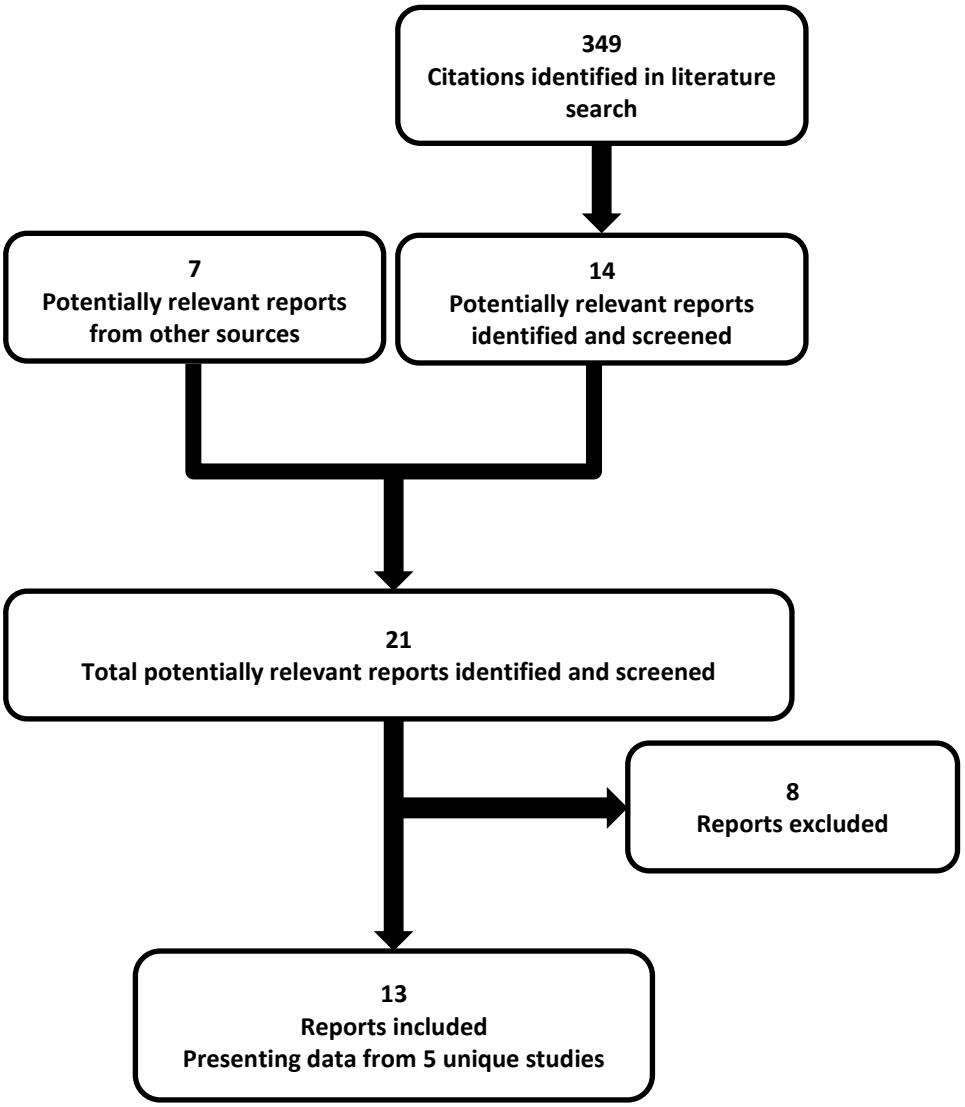

TABLE 4: DETAILS OF INCLUDED STUDIES: HEALTH CANADA PIVOTAL TRIALS

		Study 1	Study 2	Study 3
Designs & Populations	**Study Design**	OL, randomized, phase III	OL, randomized, phase III	OL, single-group, nonrandomized, phase III
	Locations	US (2 sites)	US (7 sites)	Mexico (3 sites)
	Randomized (N)	442 152[a]	966 218[a]	1,000 569[a]
	Inclusion Criteria	Healthy women ≥ 18 years (or ≥ 16 years with parental consent) seeking elective abortion with pregnancies ≤ 56 days from LMP	Healthy women ≥ 18 years seeking elective abortion with pregnancies ≤ 63 days from LMP	Women of reproductive age ≥ 14 years requesting termination of pregnancies ≤ 63 days from LMP
	Exclusion Criteria	Ectopic pregnancy, IUD, CRF, CS therapy, hemorrhagic disorder or anticoagulant therapy, inherited porphyrias		
Drugs	**Intervention**	Mifepristone: Single dose of 200 mg p.o. followed 24 h to 72 h later by Misoprostol: Single dose of 800 mcg by the buccal route	Mifepristone: Single dose of 200 mg p.o. followed 24 h to 36 h later by Misoprostol: Single dose of 800 mcg by the buccal route	Mifepristone: Single dose of 200 mg p.o. followed 24 h to 48 h later by Misoprostol: Single dose of 800 mcg by the buccal route
	Comparator(s)	Mifepristone: Single dose of 200 mg p.o. followed 24 h to 72 h later by Misoprostol: Single dose of 800 mcg by the vaginal route	Mifepristone: Single dose of 200 mg p.o. followed 24 h to 36 h later by Misoprostol: Single dose of 800 mcg by the PO route	NA
Duration	**Phase**			
	Run-in	NA	NA	NA
	Double-blind	NA	NA	NA
	Follow-up	2 to 36 days	7 to 14 days	8 days
Outcomes	**Primary End Point**	Complete abortion without surgical intervention at any time		
	Other End Points	Patient satisfaction	Effect of a second misoprostol dose, patient satisfaction, pain	Patient satisfaction
Notes	**Publications**	Middleton et al., 2005[6]	Winikoff et al., 2008[7]	Pena et al., 2014[5]

CRF = chronic renal failure; CS = corticosteroid; LMP = last menstrual period; NA = not applicable; OL = open-label; p.o. = oral.
Note: Four additional reports were included (manufacturer's submission,[19] Health Canada Reviewer's Report,[20] US FDA medical review,[21] and statistical review[22]).
[a] Number of women with gestational age ≤ 49 days since LMP reported in Mifegymiso product monograph.[4]
Source: Mifegymiso product monograph,[4] Middleton et al., 2005,[6] clinical study report,[13] Winikoff et al., 2008,[7] clinical study report,[14] Pena et al., 2014,[5] clinical study report.[15]

TABLE 5: DETAILS OF INCLUDED STUDIES: TRIALS SELECTED FOR INCLUSION

		Study 4	Study 5
Designs & Populations	**Study Design**	DB, RCT	DB, RCT
	Locations	China (1 site)	Tunisia and Vietnam (2 sites)
	Randomized (N)	90 48[a]	441 230[a]
	Inclusion Criteria	Healthy women ≥ 18 years requesting termination of pregnancies ≤ 63 days after LMP	Healthy women ≥ 15 years presenting to maternity hospital for early medical abortion of intrauterine pregnancy ≤ 63 days after LMP
		Contraindication or allergy, IUD, Hg < 100 g/L, breastfeeding, or multiple pregnancies	Contraindication or allergy, IUD, ectopic pregnancy, chronic adrenal failure, CS therapy, hemorrhagic disorder or concurrent anticoagulation, porphyrias
Drugs	**Intervention**	Mifepristone: Single dose of 200 mg p.o. followed 48 h later by Misoprostol: Single dose of 800 mcg by the buccal route plus PL by SL route	Mifepristone: Single dose of 200 mg p.o. followed 24 h later by Misoprostol: Single dose of 800 mcg by the buccal route plus PL 3 h later
	Comparator(s)	Mifepristone: Single dose of 200 mg p.o. followed 48 h later by Misoprostol: Single dose of 800 mcg by the SL route and PL by buccal route	PL: Single dose p.o. followed 24 h later by Misoprostol: 1,600 mcg administered as two doses of 800 mcg by the buccal route given 3 h apart
Duration	**Phase**		
	Run-in	NA	NA
	Double-blind	Single-dose administration	Single-dose administration
	Follow-up	14 to 43 days	7 ± 2 days
Outcomes	**Primary End Point**	Proportion of women with fever (> 38°C)	Complete uterine evacuation without surgical evacuation for any reason
	Other End Points	Complete abortion rate, induction-abortion interval, bleeding on day 15	Complete abortion, ongoing pregnancy, nonviable pregnancy or gestational sac, incomplete abortion (all by gestational age), characterization and satisfaction with the procedure
Notes	**Publications**	Chai et al., 2013[8]	Blum et al., 2012[9] Ngoc et al., 2011[10]

DB = double-blind; CS = corticosteroid; Hg = hemoglobin; LMP = last menstrual period; NA = not applicable; p.o. = oral; PL = placebo; RCT = randomized controlled trial; SL = sublingual.

Note: Four additional reports were included (manufacturer's submission,[19] Health Canada Reviewer's Report,[20] US FDA medical review,[21] and statistical review[22]).

[a] Number of women with gestational age ≤ 49 days since LMP reported in publications.

Source: Chai et al., 2013,[8] Blum et al., 2012,[9] Ngoc et al., 2011.[10]

3.2 Included Studies

3.2.1 Description of Studies

Five prospective trials met the selection criteria for inclusion in the systematic review. Three open-label trials were considered pivotal by Health Canada, as detailed in Table 4: Study 1 (N = 442), Study 2 (N = 966), and Study 3 (N = 1,000). As well, two double-blind trials were identified from the clinical literature search (Table 5): Study 4 (N = 90) and Study 5 (N = 441). Three trials (Studies 1, 2, and 4) were randomized, parallel-group comparisons of different routes of administration (ROA) of misoprostol (i.e., oral, vaginal, and SL) with buccal misoprostol, all following a single oral dose of mifepristone. Study 5 was also a randomized trial comparing oral mifepristone and buccal misoprostol with buccal misoprostol alone. Randomization was not stratified by any variables in any of the trials. Study 3 was a nonrandomized, single-arm trial of the Health Canada–approved mifepristone and misoprostol regimen. All trials enrolled women of child-bearing age (14 years and older) who voluntarily sought medical abortion for a pregnancy with gestational age of up to 56 to 63 days since the last menstrual period (LMP). In all the trials, a subpopulation of women with pregnancies ≤ 49 days based on LMP (per the Health Canada–approved regimen for Mifegymiso) could be identified. All five trials are published in the peer-reviewed medical literature.[5-10]

Study 1 was an open-label, randomized trial conducted at two US sites in healthy pregnant women 18 years of age or older (or at least 16 years with parental consent) seeking abortion with a pregnancy of gestational age up to 56 days since LMP, as confirmed by vaginal probe ultrasonography. All women received a single dose of mifepristone 200 mg at the study site and then were randomized in blocks of eight to either buccal or vaginal misoprostol according to a computer-generated randomization scheme. Women received a sealed envelope with their randomization assignment, and misoprostol 800 mcg was dispensed to the women for later use (one to two days) via the assigned route at home. Women returned to the study site at their discretion for follow-up and vaginal ultrasonography between day 1 of using misoprostol and 15 days after taking mifepristone (i.e., days 2 to 15). If the pregnancy was ongoing before day 15, the woman was instructed to return on day 15 for a second evaluation. If the pregnancy was still viable on day 15, a uterine aspiration was performed. If there was a nonviable gestational sac, the woman had the option to wait until day 36 to see if completion would be spontaneous, and if not, the woman was given a surgical completion. Once a complete abortion was confirmed, an exit interview was conducted.

Study 2 was an open-label, randomized trial conducted at seven US sites in healthy pregnant women at least 18 years of age seeking medical abortion of a pregnancy with gestational age up to 63 days since LMP (as confirmed by LMP, clinical examination, and/or ultrasonography). On day 1, women took mifepristone 200 mg at the study site and then were provided with 800 mcg misoprostol to be taken orally or buccally, according to randomization assignment, 24 to 36 hours later at home. Allocation to study group was done using a computer-generated randomization sequence (using random blocks of eight and stratified by study centre). Sealed opaque envelopes containing the assignments were given to study participants in numerical sequence. Both providers and study participants became aware of group assignment only once the envelopes were opened. Women returned to the study site seven to 14 days after taking mifepristone for clinical assessment (including transvaginal ultrasonography except at one site where beta-human chorionic gonadotropin levels were routinely monitored). In the case of ongoing pregnancies, women were offered suction aspiration. Women with nonviable pregnancies (e.g., sac or evidence of products of conception but no gestational growth and no cardiac activity on ultrasonography) could opt for suction aspiration, expectant management, or a second misoprostol dose via the same route as the previous dose. If either of the latter two options were chosen, women were asked to return seven days later. If a persistent nonviable pregnancy was diagnosed at the extended

follow-up visit, a suction aspiration was recommended. Providers could also intervene surgically if deemed medically necessary at any time.

Study 3 was an open-label, nonrandomized (single-arm) trial conducted at three sites in Mexico in women of reproductive age (≥ 14 years) seeking abortion of pregnancies of up to 63 days' gestation, as measured from LMP, clinical evaluation, and ultrasonography. As detailed in Figure 2, on day 1, women took 200 mg mifepristone orally in the study centre and then were given 800 mcg misoprostol to be taken via the buccal route at home 24 to 48 hours after mifepristone. Women were requested to return to the study site eight days after study enrolment for a clinical examination and ultrasonography to determine abortion status. In the case of continuing pregnancies, suction aspiration was offered. In the case of nonviable pregnancies (e.g., persistent gestational sac, retained products of conception, or bleeding), women were offered a second dose of misoprostol, suction aspiration, or expectant management, and were scheduled to return one week later. If the nonviable pregnancy continued, suction evacuation was performed. Women were required to complete an exit interview before study discharge.

FIGURE 2: DESIGN OF STUDY 3

Source: Clinical study report from the manufacturer.[15]

Study 4 was a double-blind, randomized, placebo-controlled trial conducted at a single site in Hong Kong comparing two ROAs of misoprostol (buccal and SL) in healthy women 18 years and older with pregnancies of up to 63 days' gestation (confirmed by transvaginal ultrasonography). On day 1, women were given 200 mg mifepristone in the presence of medical or nursing staff. After 48 hours, women

returned to the study site and were randomly assigned to either buccal or SL misoprostol according to a computer-generated program. Women received packages according to their assignment that contained four 200 mcg misoprostol tablets to be taken orally and four matching placebo tablets to be taken SL (or vice versa). Women were instructed to put four tablets of misoprostol or placebo first under the tongue and then to hold two tablets in each cheek pouch under supervision by the study nurse who was blinded to the treatment. Women stayed under observation, underwent vaginal examination at the end of four hours, and were interviewed regarding the treatment-emergent adverse events (TEAEs) experienced. Women who did not have heavy bleeding or severe pain were allowed to go home, but were required to return on day 15 for clinical assessment, ultrasonography, and blood sampling for hemoglobin level. If the pregnancy was ongoing, vacuum aspiration could be arranged without a further attempt with misoprostol. If an incomplete or missed abortion had occurred, women were observed unless there was heavy bleeding. Study participants were then followed up again on day 43 for return of menses.

Study 5 was a double-blind, randomized, placebo-controlled trial in women 15 years and older with pregnancies up to 63 days from LMP presenting for medical abortion at two large maternity hospitals in Tunisia (n = 193) or Vietnam (n = 248). Eligible participants were randomly allocated to either of the two treatment groups using a computer-generated random sequence. All staff, providers, and study participants were blinded to treatment, and all participants received an envelope containing study medication. Women in the combined mifepristone and misoprostol group received 200 mg mifepristone on day 1, and 800 mcg of buccal misoprostol followed three hours later by placebo on day 2. Women in the misoprostol-only group received placebo on day 1 and 1,600 mcg of buccal misoprostol administered as two 800 mcg doses given three hours apart on day 2. All women were scheduled for a follow-up appointment one week ± two days later. At the follow-up, abortion status was assessed by clinical examination and/or transvaginal ultrasonography. If there were ongoing pregnancies, immediate surgical evacuation was offered. Women with a persistent nonviable pregnancy or gestational sac were given the choice of immediate surgical completion or a second 800 mcg buccal dose of misoprostol and waiting another week to see whether the products would evacuate spontaneously. Women who presented with retained products of conception at the second follow-up visit underwent a vacuum aspiration.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

All five included trials enrolled healthy women of reproductive age who were voluntarily seeking termination of intrauterine pregnancies with gestational age up to 56 to 63 days since LMP. In general, women had to be eligible for medical abortion following clinical examination and had to be willing to undergo a surgical completion, if necessary, to complete the abortion. Women were also required to provide contact information for follow-up purposes.

Key exclusion criteria included gestational age beyond that specified in the protocol (i.e., > 63 days), ectopic pregnancy, IUD, long-term corticosteroid treatment, bleeding disorders, porphyrias, anticoagulant therapy, or other contraindications or hypersensitivity to study drugs. In Study 4, women with a hemoglobin level < 100 g/L, who were breastfeeding, or had multiple pregnancies were excluded.

b) Baseline Characteristics

Baseline demographic characteristics appeared to be balanced between treatment arms in individual studies. The mean age of enrolled women ranged from 25 to 29 years, although Study 3 and Study 5 enrolled younger patients (i.e., 13 and 15 years and older, respectively), whereas the other three trials enrolled only adult women (i.e., 18 years of age and older). The majority of women had completed at

least a high school education and were single, with the exception of Study 5, in which more than 75% of women were married. Most women had had a prior pregnancy, although, in Study 2 and 3, only mean gravida was reported, which was between two and three (range: one to 11). In Studies 1 and 4, in which parity was reported, between 40.0% and 71.1% of women had had a prior birth. Overall, 9.7% to 60.1% of women had had a previous induced abortion. Mean gestational age on study entry ranged from 47 days to approximately 50 days in Studies 1 and 2, and between 48.9% and 56.9% of women in Studies 3, 4, and 5 had a pregnancy with gestational age ≤ 49 days from LMP.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Study 1		Study 2		Study 3	Study 4		Study 5[a]	
	Miso 800 mcg Buccal N = 223	Miso 800 mcg Vaginal N = 219	Miso 800 mcg Buccal N = 434	Miso 800 mcg Oral N = 435	Miso 800 mcg Buccal N = 1,000	Miso 800 mcg Buccal N = 45	Miso 800 mcg SL N = 45	Miso 800 mcg Buccal N = 220	Miso 1,600 mcg Buccal N = 221
Age, years									
Mean (SD or range)	26 (18 to 46)	26 (17 to 45)	26.7 (6.1)	25.8 (5.8)	25.4 (13-45)	28.6 (7.3)	26.7 (7.2)	29 (6.2)	29 (6.5)
Education level	NR	NR			NR	NR	NR		
< High school			32 (7.4)	33 (7.6)				36 (16.4)	43 (19.5)
High school			227 (52.3)	231 (53.1)				139 (63.2)	128 (57.9)
University			139 (32.0)	147 (33.8)				45 (20.5)	50 (22.6)
Postgraduate			30 (6.9)	17 (3.9)					
Unknown			6 (1.4)	7 (1.6)					
Education, years									
Mean (range)	13 (8 to 23)	13 (9 to 19)	NR	NR				NR	NR
Married, n (%)	40 (17.9)	37 (16.9)	73 (16.8)	61 (14.1)	NR	NR	NR	178 (80.9)	170 (76.9)
Gravidity									
Mean (range)	NR	NR	3 (1 to 11)	3 (1 to 13)	2.3 (1 to 7)			2.98 (1 to 9)	2.74 (1 to 9)
Prior pregnancy, n (%)	NR	NR	NR	NR	NR	26 (57.8)	20 (44.4)	171/217 (78.8)	158/218 (72.5)
≥ 2 pregnancies, n (%)	189 (84.8)	192 (87.7)	NR	NR	NR	NR	NR	NR	NR
Parity (≥ 1), n (%)	145 (65.9)	157 (71.7)	NR	NR	NR	22 (48.9)	18 (40.0)	NR	NR
Prior induced abortions (≥ 1), n (%)	134 (60.1)	131 (59.8)	201 (46.4)	219 (50.5)	97 (9.7)	15 (33.3)	13 (28.9)	52 (23.6) Surgical 38 (17.4) Medical[b]	48 (21.7) Surgical 35 (15.8) Medical

Characteristic	Study 1		Study 2		Study 3	Study 4		Study 5[a]	
	Miso 800 mcg Buccal N = 223	Miso 800 mcg Vaginal N = 219	Miso 800 mcg Buccal N = 434	Miso 800 mcg Oral N = 435	Miso 800 mcg Buccal N = 1,000	Miso 800 mcg Buccal N = 45	Miso 800 mcg SL N = 45	Miso 800 mcg Buccal N = 220	Miso 1,600 mcg Buccal N = 221
Gestational age, days									
Mean (SD or range)	47 (30 to 62)[c]	47 (31 to 56)	49.9 (8.1)	49.7 (8.3)	NR	50.3 (7.5)	49.6 (7.2)	NR	NR
n (%)									
< 49 days					569 (56.9)	22 (48.9)	26 (57.8)	109 (49.5)	121 (54.8)
50 to 56 days					252 (25.2)			74 (33.6)	70 (31.7)
57 to 63 days					177 (17.7)	23 (51.1)[d]	19 (42.2)[d]	27 (12.3)	27 (12.2)
> 64 days					2 (0.2)			NR	NR

Miso = misoprostol; NR = not reported; SD = standard deviation; SL = sublingual.

[a] In Study 5 patients in the Miso 800 mcg buccal group received mifepristone 200 mg followed 24 hours later by 800 mcg misoprostol by the buccal route. Patients in the Miso 1,600 mcg group received placebo followed 24 hours later by two doses of 800 mcg misoprostol by the buccal route given 3 hours apart.

[b] Data are missing for 2 participants.

[c] One woman with a pregnancy > 56 days LMP was mistakenly enrolled.

[d] Gestational age was reported only as ≤ 49 days or 50 to 63 days.

Source: Middleton et al., 2005,[6], clinical study report[13], Winikoff et al., 2008,[7] clinical study report[14], Pena et al., 2014[5], clinical study report[15], Chai et al., 2013,[8] Blum et al., 2012,[9] Ngoc et al., 2011.[10]

3.2.3 Interventions

In all five included trials, the intervention was the Health Canada–approved regimen of a single oral dose of 200 mg mifepristone followed by a single buccal dose of 800 mcg misoprostol (four 200 mcg tablets) 24 to 48 hours later, although Study 1 permitted the misoprostol dose to be administered up to 72 hours later. In all of the trials, the dose of mifepristone (or matched placebo in Study 5) was administered under observation at the study site. In all of the trials (except Study 4), women were given the dose of misoprostol to take at home. Women were instructed to administer buccal misoprostol (or matched placebo in Studies 4 and 5) by holding the tablets inside each cheek pouch for 20 to 30 minutes and to swallow any remaining fragments after this time. Women who received vaginal misoprostol were instructed to place all four misoprostol tablets high into the vagina with a finger. In Study 4, women received packages of misoprostol and matched placebo tablets and were instructed to put four tablets first under the tongue, which would dissolve in 10 to 15 minutes, then to hold two tablets in each cheek pouch for 30 minutes and to swallow any remaining fragments under the supervision of the research nurse. In all of the trials, it appeared that misoprostol regular-release oral tablets were used regardless of the ROA (buccal, vaginal, oral, or SL), rather than specialized formulations intended for the specific ROA.

Depending on the individual study, participants were also given pain medication (e.g., acetaminophen with or without codeine) to use at home, if necessary, or prescriptions for oral narcotic analgesics for pain management as well as antinausea and antidiarrheal medications. Women with rhesus-negative blood were given anti-D immune globulin.

3.2.4 Outcomes

The primary outcome in Studies 1, 2, 3, and 5 was complete abortion (also referred to as “success”), which was defined as a complete abortion without surgical intervention at any time. In all of the trials, complete abortion was confirmed by vaginal ultrasonography, with the exception of one study site in Study 2, where beta-human chorionic gonadotropin levels were routinely monitored and ultrasonography was employed only when needed. The study procedures varied across the individual trials in the case of an ongoing pregnancy, persistent nonviable pregnancy, gestational sac, or retained products of conception that were detected at a follow-up visit, as described in detail in Section 3.2.1. In Study 4, the primary outcome was the proportion of women with fever, although a secondary outcome measure was complete abortion rate.

Women completed diary cards or questionnaires, or were directly questioned at each study visit regarding TEAEs experienced from the medications, bleeding and cramping, pain medication required, and any other medications used. In Studies 1, 2, 4, and 5, women were given a diary card to record any TEAEs, extent and duration of bleeding, and pain or antinausea medications used at home, although the specific items to be recorded differed among the trials. In Study 3, TEAEs were reported by women only during an exit interview before discharge, and the severity of each TEAE was classified on a three-point scale (mild, moderate, or severe). Women also received instructions on when to return for a follow-up visit and where to seek 24-hour help in case of concerns or emergencies.

In Studies 1, 2, and 3, an exit interview was conducted following confirmation of complete abortion. In Study 1, the publication reported only that, at the exit interview, patient satisfaction was assessed using a five-point Likert scale ranging from “very unsatisfied” to “very satisfied,” whereas women’s perception of pain was measured on a seven-point visual pain chart.[6,13] In Study 2, women reported their perception of the acceptability of the procedure, presumably during semi-structured interviews at the follow-up visit according to a Likert scale, although this was not specifically reported in the

publication.[7,14] In Study 3, women rated their pain experience during treatment using a seven-point Likert scale that depicted a series of faces ranging from sad to neutral to happy. Each face represented a grade of pain severity, with the happiest face representing no pain and the saddest face representing the worst pain imaginable. Study 4 did not report on patient acceptance or satisfaction. Although Study 5 did report results for patient satisfaction and characterization of the procedure outcomes, the methodology or study procedures used to acquire these data were not provided. It was only stated that, after complete abortion, women were interviewed to gauge acceptability of and satisfaction with the treatment.[10]

3.2.5 Statistical Analysis

In Study 1, the sample size was based upon 221 women in each treatment group, which would achieve 80% power to detect a difference in efficacy of 7% between the two treatment groups. Efficacy was assumed to be 97% in the vaginal group and 90% in the buccal group using a one-sided chi-square test without continuity correction, at the 0.05 significance level, although the source of the efficacy assumptions was not specified. The primary outcome (success) between groups and the secondary outcome (patient satisfaction) were assessed using the Pearson chi-square test. Descriptive statistics were used to summarize patients' demographic and clinical characteristics as well as all other study outcomes (e.g., reasons for surgical intervention, pain scores, TEAEs).

In Study 2, the sample size was based on 105 women with pregnancies of gestational age ranging from 57 to 63 days in each study group in order to estimate efficacy at 93% with a 95% confidence interval (CI) of ± 5% (assuming a 5% rate of loss to follow-up). Based on US abortion clinic statistics, it was estimated that 15% to 20% of pregnancies in all study participants would fall in the gestational age range of 57 to 63 days, resulting in anticipated enrolment of a total of 1,200 women.[7,14] Therefore, with at least 425 women per group, and assuming 95% efficacy for the buccal misoprostol regimen, it was determined that a 5% difference between the study arms could be detected with 80% power at the 95% CI, a difference the study investigators considered to be clinically important for formulating clinical practice guidelines.[7,14]

An interim analysis was conducted to assess safety in Study 2, after approximately 50% of the study sample had completed participation, but it was unclear which safety outcome(s) were considered. The normality of continuous variables was assessed by graphic display. The primary outcome (success) was assessed both using both per-protocol (PP) and intention-to-treat (ITT) analyses; however, according to the publication, since no significant differences were found using the chi-square test, only results for the PP analysis were presented.[7,14] For the final analysis of the primary outcome, the alpha was reduced to 0.0479 as a result of the interim analysis, according to the O'Brien and Fleming method.[23] Secondary outcomes were compared using the chi-square test or Fisher's exact test. The impact of gestational age on the primary and secondary outcomes was assessed by the chi-square test for trend, and post hoc, pairwise comparisons were conducted using Tukey's honestly significant difference (HSD) test, when results were significant. For the secondary analyses, two-tailed $P < 0.05$ was considered statistically significant.

In Study 3, the sample size was based on the results of another US clinical trial (N = 847) that demonstrated 96% efficacy with 200 mg of mifepristone and 800 mcg buccal misoprostol for termination of pregnancies of gestational age up to 63 days since LMP.[24] Thus, a sample of 500 women was considered large enough to demonstrate efficacy of almost 95% with a CI of ± 2%. Because of the participation of several study sites, the sample size was doubled (N = 1,000) to compensate for variations among sites, personnel, and patient populations, and to account for loss to follow-up

(estimated at 15%). As this was a single-arm trial with assessment at only one time point, the results for the primary and secondary outcomes are presented as mean (range or SD) or number (percentage).

In Study 4, the sample size was based upon the difference in proportion of women with fever. Based on results of previous studies, one of which was Study 2,[7,14] it was determined that a sample size of 84 women would result in the study having 80% power to detect a difference in the proportion of women with fever (the primary outcome) at a 5% level of significance. The total sample was 90 women, which permitted a 5% default rate. Differences in continuous variables were analyzed using the Student's t-test for normally distributed data and the Mann–Whitney U test for skewed data. For differences in categorical variables, the chi-square test and Fischer's exact test were used, as appropriate. Two-tailed $P < 0.05$ was considered statistically significant. All outcomes were analyzed on an ITT basis.

In Study 5, the sample size was based on the assumption that the mifepristone and misoprostol combination would be 95% effective and that two doses of buccal misoprostol administered three hours apart would be approximately 88% effective. Thus, a 7% difference between the two groups was considered clinically meaningful. As a result, a sample size of 376 would provide 80% power given an alpha value of 0.05 for a one-sided test. The estimated efficacy of misoprostol alone was assumed to be 83% (based on results with other ROA at three-hour time intervals). In order to account for loss to follow-up (estimated at approximately 15%), the study planned to enrol 432 women (216 per group). In the end, 441 women were enrolled as concurrent recruitment was ongoing in two countries. The study data were entered separately in each of the two countries, and clean datasets merged for analysis in the US. The two treatment groups were compared using t-tests or the Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact tests for categorical variables. The main study outcomes (e.g., success, reasons for surgical intervention, patient satisfaction, certain TEAEs) were compared using relative risk (RR), 95% CIs, and *P* values where $P < 0.05$ was considered statistically significant.

a) Analysis Populations

Details of the analyses and safety populations in the included trials are provided in Table 7. Across all the trials, efficacy (complete abortion rate) was analyzed in the population of patients with "cases analyzed," which was defined as patients with complete data for whom an outcome was known (essentially, a PP population). The safety population consisted of only those patients for whom safety data could be obtained based on diary cards, questionnaires, and exit interviews.

3.3 Patient Disposition

Details of patient disposition across the included trials are provided in Table 7. The only reason for discontinuation in all the trials was loss to follow-up (i.e., patients who did not return for the follow-up visit despite attempts to contact the patient via telephone and registered letter). The proportion of patients who discontinued/were lost to follow-up ranged from 0.9% to 9.7% across the treatment arms of individual trials. The proportion of patients lost to follow-up was highest in Study 2 (9.7% and 9.3% in the misoprostol buccal and oral arms, respectively) compared with 0.9% to 4.4% in the other treatment arms across studies. In Study 4, two patients were lost to follow-up in the misoprostol SL group, as they did not return for follow-up on day 43; however, these patients were included in the analysis population as the outcome of their pregnancies was known.

TABLE 7: PATIENT DISPOSITION

	STUDY 1		STUDY 2		STUDY 3	STUDY 4		STUDY 5	
	MISO 800 MCG BUCCAL	MISO 800 MCG VAGINAL	MISO 800 MCG BUCCAL	MISO 800 MCG ORAL	MISO 800 MCG BUCCAL	MISO 800 MCG BUCCAL	MISO 800 MCG SL	MISO 800 MCG BUCCAL	MISO 1,600 MCG BUCCAL
Screened, N	NR		NR		NR	102		NR	
Randomized, N	223	219	484	482	1,000[a]	45	45	220	221
Discontinued, n (%)	7 (3.1)	6 (2.8)	47 (9.7)	45 (9.3)	29 (2.9)	0	0		
Lost to follow-up	7 (3.1)	6 (2.8)	47 (9.7)	45 (9.3)	29 (2.9)	0	2 (4.4)[b]	2 (0.9)	0
ITT, n (%)	223[c]	219[c]	481[d]	480[d]	1,000	45	45	217[e]	218[e]
PP/Cases analyzed[f]	216	213	421[g]	426[g]	971	45	45	210[h]	218
Safety, n (%)	216	213	414[i]	416/420[i]	969[j]	45	45	209[k]	218

ITT = intention-to-treat; NR = not reported; PP = per-protocol; SL = sublingual.

[a] Study 3 was a nonrandomized study therefore 1,000 patients were enrolled in the study but were not randomized to treatment.

[b] Two patients were lost to follow-up on day 43 but still included in cases analyzed.

[c] One woman randomized to the vaginal group received misoprostol buccally and one woman randomized to the buccal group received misoprostol vaginally. One woman randomized to the vaginal group opted for a surgical procedure before using misoprostol due to hyperemesis and was included as a failure.

[d] Three patients randomized to the buccal group and 2 patients randomized to the oral route withdrew before receiving misoprostol.

[e] Three patients in each group did not receive study drug or changed their mind about taking the study drugs.

[f] Cases analyzed are those patients for whom data are complete and were analyzed for efficacy.

[g] Of 434 patients in the buccal group and 435 patients in the oral group who returned for follow-up, 3 patients and 9 patients, respectively, were excluded from the efficacy analysis for protocol deviation (i.e., wrong route, time or dose, or ectopic pregnancy).

[h] Five patients did not have 1 week follow-up in addition to the 2 patients who were lost to follow-up.

[i] The data are the total number of patients based on safety results reported from diary entry/exit interview.

[j] Two patients did not complete the exit interview.

[k] Data are missing as not all patients responded to all questions.

Source: CONSORT diagrams for Study 1, 2, and 3,[19] Middleton et al., 2005,[6] clinical study report,[13] Winikoff et al., 2008,[7] clinical study report,[14] Pena et al., 2014,[5] clinical study report,[15] Chai et al., 2013,[8] Blum et al., 2012.[9]

3.4 Exposure to Study Treatments

Due to the single-dose nature of the treatment regimen, all study participants (unless they withdrew before receiving study drugs) were exposed to a single oral dose of 200 mg mifepristone, followed 24 to 72 hours later with 800 mcg of misoprostol via the buccal, oral, or SL routes. In Study 5, patients in the misoprostol-only group were exposed to two doses of 800 mcg misoprostol (1,600 mcg total) through the buccal route, separated by three hours.

3.5 Critical Appraisal

a) Internal Validity

All five included studies were prospective trials with methodological strengths. With the exception of Study 3, all of the trials were randomized with appropriate methods for treatment assignment. Allocation concealment methods (i.e., use of sealed opaque envelopes in Study 2 and concealed packages in Study 4) were appropriate. It was not clear whether envelopes provided in Studies 1 and 5 were opaque, as it was only stated in the publications that a "sealed envelope" or "envelope" was provided. The use of matched placebo tablets for mifepristone and misoprostol in Studies 4 and 5 was also appropriate. Baseline demographic characteristics were generally balanced across treatment arms in individual trials, with no baseline imbalances on known characteristics. Discontinuation rates were low in all the trials, and the only reason for discontinuation was that patients were lost due to follow-up despite repeated attempts to contact the patients.

The primary sources of information and data were the publications of the five included trials and, as a result, details regarding study protocols, methodology, and data analysis were lacking. For example, in Study 1, the source of the efficacy assumptions for the sample size calculation is unknown. Across all five trials, it is unknown whether any of the subgroup analyses were specified a priori. Furthermore, randomization was not stratified by gestational age (e.g., ≤ 49 days since LMP); therefore, the subgroup analyses by gestational age are limited by the fact that randomization may not have been maintained. In all of the five trials, there was no control of secondary outcomes or adjustments made for multiplicity, nor were any of the analyses adjusted for covariates. Imputation of missing data was not carried out, and efficacy analyses were based on "cases analyzed," which was defined as patients with complete data for whom the pregnancy outcome was known, rather than a true ITT population.

Studies 1, 2, and 3 were open-label trials; therefore, both investigators and patients were aware of the treatment assignment. This may have affected study outcomes and introduced reporting bias, especially for subjective outcomes such as patient acceptability of or satisfaction with the procedure, or the incidence of TEAEs. Knowledge of the treatment allocation by study personnel could also have affected the questioning of patients at the exit interview or influenced patient management. In clinical practice, the timing and length of follow-up for medical abortion, and the propensity to intervene surgically, have an important effect on observed differences in success rates.[7,14] Both Study 4 (misoprostol arms only) and Study 5 (both mifepristone and misoprostol and misoprostol-alone arms) employed double-blind conditions.

Across all trials, the primary efficacy analyses were based on cases analyzed or the population of patients with complete data (i.e., patients with known pregnancy outcomes). It follows that success or failure rates were reported in essentially PP populations, rather than true ITT analyses. The exception to this is Study 4, in which the efficacy and safety outcomes were reported for all randomized patients. Ideally, in a trial that is designed to demonstrate superiority (as opposed to noninferiority), the analyses should be conducted in the ITT population.

The safety populations consisted of only those patients with safety data, as reported on diary cards or questionnaires, or during exit interviews. Although diary cards are a standard method of recording TEAEs, self-reporting is subject to individual variability in reporting accuracy and completion. The safety populations in the trials did not include the patients who were lost to follow-up, and those patients might have experienced TEAEs or serious adverse events (SAEs) that are not captured in the safety analyses. The proportion of patients who were lost to follow-up ranged from 0.9% to 4.4% in Studies 1, 3, 4, and 5; however, the proportion was 9.7% and 9.3% in the misoprostol buccal and oral arms, respectively, of Study 2. No reason for the larger proportion of patients who were lost to follow-up in Study 2 was provided, although it was stated in the publication that in-clinic and telephone follow-up conducted was adequate to determine that a woman's pregnancy had been terminated.[7,14]

In Study 4, patient acceptability of or satisfaction with the procedure was not included as a study outcome, which would have provided useful information on the comparison of buccal and SL misoprostol in this regard. Due to the small sample size (N = 45 per treatment group), this study may have been insufficient to capture less commonly encountered adverse events.

No data were available from the included trials for important outcomes identified in the review protocol such as health-related quality of life (HRQoL), psychiatric/psychological morbidity, or health care resource utilization. Of these, information on HRQoL would have been particularly valuable, especially in the context of evaluating the impact of medical abortion compared with surgical abortion on patients' HRQoL.

3.5.2 External Validity

According to the clinical expert consulted for this review, the baseline demographic characteristics of the patients enrolled in the five trials are representative of Canadian women voluntarily seeking abortion services in Canada.

The included trials were all based in specialized hospitals or clinic settings; therefore, the results may not be fully generalizable to a different clinical practice setting with less experienced providers. Less experienced providers such as general practitioners may be more prone to intervene surgically in the event of retained products and/or incomplete abortion compared with the experienced study personnel involved in the included trials.[10]

In Study 5, the results of the misoprostol-alone group are not generalizable to other misoprostol-alone regimens. Study 5 tested a regimen of two 800 mcg doses of misoprostol administered three hours apart via the buccal route on day 2. Outcomes may differ with other ROAs or with different time intervals between the administration of misoprostol doses. According to the clinical expert, it is common to use repeated doses of misoprostol if the initial medical abortion regimen was not successful.

No trials were identified that directly compared the Health Canada–approved regimen of mifepristone and misoprostol for medical abortion with surgical abortion, which is the primary method used for abortion in Canada. Furthermore, no trials were identified that directly compared mifepristone and misoprostol with methotrexate and misoprostol, which is the current standard of care for medical abortion in Canada. This is supported by the 2016 SOGC guideline, which states that, in the absence of mifepristone, the combination of methotrexate and misoprostol has been the most frequently prescribed regimen for medical abortion in Canada.[1]

Although the trials enrolled patients with pregnancies of gestational age up to 56 to 63 days, the success rates for women with pregnancies of gestational age ≤ 49 days from LMP (per the current Health Canada–approved indication for Mifegymiso) were consistent with those of the overall trial populations. The manufacturer has advised that a Supplemental New Drug Submission (SNDS) to extend the gestational age in the indication to 63 days is currently under review by Health Canada. Therefore, the conclusions of this review are expected to be applicable to Canadian women with gestational age up to 63 days should the SNDS be approved before completion of the review of Mifegymiso by CDR.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See 0 for detailed efficacy data.

3.6.1 Pregnancy Outcome

Across all five trials, success rates (i.e., the proportion of women with complete abortion without surgical intervention at any time) with 200 mg oral mifepristone plus 800 mcg buccal misoprostol ranged from 92.9% to 97.3% in the overall study populations (Tables 9 to 13). In all trials, with the exception of Study 5, women took an oral dose of 200 mg mifepristone followed by misoprostol 800 mcg 24 to 72 hours later via various ROAs (e.g., buccal, vaginal, oral, SL). In Study 1, there was no statistically significant difference in success rates between misoprostol administered buccally (94.9%) and misoprostol administered vaginally (93.4%); however, in Study 2 the difference between misoprostol administered buccally (96.2%) and misoprostol administered orally (91.3%) was statistically significant (RR 0.95; 95% CI, 0.92 to 0.98; $P < 0.048$; Table 10). For the outcome of success, an RR < 1 indicates that the event is less likely to occur in the comparator group (oral misoprostol) than in the intervention group (buccal misoprostol). Study 3 was a single-arm trial that included the largest number of cases analyzed (N = 971) in a single study, and it reported a success rate of 97.3%. In the publication for Study 4, success rates for buccal (95.6%) and SL (97.8%) misoprostol were reported to be not statistically significantly different; however, no *P* value was provided.[8] In Study 5, the success rate following 200 mg oral mifepristone and 800 mcg buccal misoprostol (92.9%) was higher than with 1,600 mcg buccal misoprostol alone (78.0%), and the difference was statistically significant (RR 0.84, 95% CI, 0.78 to 0.91; $P < 0.001$).

Success rates in women with gestational age ≤ 49 days were consistent with those in the overall populations in all the trials. The success rates following 200 mg oral mifepristone plus 800 mcg buccal misoprostol in this subpopulation ranged from 95.2% to 100.0% (Tables 9 to 13). The only statistically significant difference in success rates for women with gestational age ≤ 49 days was observed in Study 5 (i.e., 96.3% for mifepristone and misoprostol versus 78.5% for misoprostol alone; RR 0.82; 95% CI, 0.74 to 0.90; $P < 0.001$). The RR < 1 indicates that the event is less likely to occur in the comparator group than in the intervention group (i.e., buccal misoprostol 800 mcg).

There were no statistically significant differences in success rates by gestational age in Studies 1, 3, or 4. In Study 2, however, the difference in success rate was statistically significantly different only for women with pregnancies of gestational age 57 to 63 days (i.e., 94.8% with buccal versus 85.1% with oral misoprostol; RR 0.90; 95% CI, 0.82 to 0.98; $P < 0.048$; Table 10). In Study 5, as noted earlier, although the difference in success rates between treatment arms for women with gestational age ≤ 49 days was statistically significant, the difference between arms for either gestational age 50 to 56 days or 57 to 63 days was not.

Following 200 mg oral mifepristone and 800 mcg misoprostol administered via the various ROAs, failure rates in the overall study populations ranged from 0% to 7.1% with buccal misoprostol compared with 6.6% (vaginal misoprostol), 8.7% (oral misoprostol), 2.2% (SL misoprostol), and 22.0% with 1,600 mcg misoprostol alone (Tables 9 to 13). The difference in failure rates was only compared statistically in Study 2, in which the difference was statistically significant: buccal misoprostol had a lower failure rate (3.8%) compared with oral misoprostol (8.7%) (RR 2.29; 95% CI, 1.29 to 4.04; $P < 0.048$).

The rates of ongoing pregnancies were compared in the overall study populations and by gestational age in Studies 2 and 5. In Study 2, the rate of ongoing pregnancies was statistically significantly different in the overall study population, which was 1.0% with buccal misoprostol versus 3.5% with oral misoprostol (RR 3.71; 95% CI, 1.24 to 11.07; $P < 0.048$; Table 10). In women with pregnancies of gestational age 57 to 63 days, the difference in ongoing pregnancy rates was also statistically significant: 1.7% for buccal misoprostol versus 7.9% with oral misoprostol (RR 4.54; 95% CI, 1.0 to 20.55; $P < 0.048$). In Study 5, the rate of ongoing pregnancy was statistically significantly different in the overall study population: 1.4% with mifepristone and misoprostol versus 13.8% with misoprostol alone (RR 9.63, 95% CI, 2.98 to 31.09; $P < 0.001$; Table 13). In women with pregnancies of gestational age 50 to 56 days, the difference in ongoing pregnancy rates was also statistically significant: 2.7% for mifepristone and misoprostol versus 15.7% with misoprostol alone (RR 5.81; 95% CI, 1.34 to 25.31; $P < 0.006$).

3.6.2 Complication Rates

Rates of complications (e.g., bleeding, infection, pain), as identified in the review protocol, were not consistently reported in the included trials.

In Study 1, complications were reported in five women in the misoprostol buccal group (i.e., persistent vomiting requiring intravenous [IV] fluids and anti-emetics [n = 1], pain requiring IV pain medication [n = 1], heavy bleeding requiring IV fluids or oral antibiotics [n = 2], and heavy bleeding requiring uterine aspiration and a blood transfusion [n = 1]). In the misoprostol vaginal group, there were also five complications (i.e., shortness of breath requiring reassurance [n = 1], pelvic tenderness/endometritis requiring oral antibiotics [n = 3], pelvic tenderness and hospitalization for suspected pelvic infection requiring uterine aspiration and antibiotics [n = 1]).

In Study 2, 26 women (3.0%) in total made visits to an emergency room for pain and bleeding during the study period (n = 12 from the buccal group and n = 14 from the oral group), of which 21 were not admitted. Three women from the buccal group were hospitalized for reasons unrelated to the study protocol (i.e., pulmonary embolus, ruptured ectopic pregnancy, and right hip pain).

In Study 3, 17 women (1.7%) visited other health care facilities for bleeding or pain or a combination of the two (n = 13), anxiety (n = 2), and fainting or tachycardia (n = 2). Twelve women visiting other health care facilities underwent D&C, three were reassured and received no additional treatment, and two were offered but did not receive D&C and did not report any TEAEs. No serious complications were reported.

In all five trials, specific data on the actual amount or duration of bleeding or pain were not available. Rather, in Studies 2, 3, and 5, upon study completion, women were questioned regarding the amount of bleeding or pain they experienced relative to their expectations. The results for these outcomes are provided in Tables 15, 16, and 19, as these were the only data available. Across these studies, the proportion of women who rated the amount of bleeding as “less than expected” ranged from 28.9% to 34.0% with 200 mg oral mifepristone and 800 mcg buccal misoprostol compared with 28.3% (with 800

mcg oral misoprostol) and 26.7% (with 1,600 mcg misoprostol alone). Those who rated the amount of bleeding as "same as expected" ranged from 35.4% to 43.6% (200 mg oral misoprostol and 800 mcg buccal misoprostol) compared with 44.0% (800 mcg oral misoprostol) and 30.1% (1,600 mcg misoprostol alone). Those who rated the amount of bleeding as "more than expected" ranged from 27.0% to 30.6% (200 mg oral mifepristone and 800 mcg buccal misoprostol) compared with 26.0% (800 mcg oral misoprostol) and 43.2% (1,600 mcg misoprostol alone).

Bleeding times in Studies 1 and 2 in women with pregnancies of gestational age ≤ 49 days were reported in the Mifegymiso product monograph[4] (Table 17). In Study 1, the mean (standard deviation [SD]) days of heavy bleeding was 2.3 (2.3), of normal bleeding was 5.1 (2.9), and of spotting was 3.5 (2.5). In Study 2, the mean (SD) days of total bleeding time was 10.8 (3.9), whereas heavy bleeding lasted for a mean (SD) of 2.0 (2.1) days, normal bleeding for 4.3 (2.8) days, and spotting for 4.6 (3.2) days. One patient each in Studies 1 and 3 required a blood transfusion for excessive bleeding.[4] In Study 4, 66.7% (95% CI, 51.1 to 80.0) of women in the buccal misoprostol group and 73.3% (95% CI, 53.1 of 85.4) of women in the SL misoprostol group reported bleeding on day 15; the difference was not statistically significant (P = 0.49; Table 18). Despite this, mean (SD) hemoglobin levels did not appear to change over the duration of the study from day 1 (121 g/L [8.6 g/L] and 122 g/L [9.8 g/L]) to day 43 (123 g/L [11.5 g/L] and 124 g/L [10.0 g/L]), in the buccal and SL misoprostol arms, respectively (Table 18).

The proportion of women who rated the amount of pain as "less than expected" ranged from 26.3% to 31.9% with 200 mg oral mifepristone and 800 mcg buccal misoprostol compared with 38.6% (800 mcg oral misoprostol) and 33.2% (1,600 mcg misoprostol alone). The results for these outcomes are provided in Tables 15, 16, and 19. Those who rated the amount of pain as "same as expected" ranged from 25.0% to 38.8% (200 mg oral misoprostol and 800 mcg buccal misoprostol) compared with 34.3% (800 mcg oral misoprostol) and 22.6% (1,600 mcg misoprostol alone). Those who rated the amount of pain as "more than expected" ranged from 29.9% to 46.0% (200 mg oral mifepristone and 800 mcg buccal misoprostol) compared with 25.7% (800 mcg oral misoprostol) and 44.2% (1,600 mcg misoprostol alone). The only statistically significant difference between treatment arms was in Study 2, in which 29.6% of all women in the buccal misoprostol group compared with 38.6% of all women in the oral misoprostol group rated their pain as "less than expected" (P < 0.05; Table 15).

3.6.3 Other Outcomes

Patient satisfaction data are summarized in Appendix 4. There were no results reported in the included trials for the following efficacy outcomes identified in the review protocol: HRQoL, psychiatric/psychological morbidity, and health care resource utilization.

3.7 Harms

Only those harms identified in the review protocol are reported below (2.2.1, Protocol). See 0 for detailed harms data.

3.7.1 Adverse Events

The proportion of overall patients who experienced TEAEs was reported only in Studies 2 and 3 (Table 8). In both trials, the majority of patients experienced TEAEs: 94.9% in the buccal misoprostol group and 97.3% in the oral misoprostol group in Study 2, and 88.5% overall in Study 3. The most consistently reported TEAE across all the included trials was nausea, which ranged from 34.2% to 75.1% with 200 mg oral mifepristone and 800 mcg buccal misoprostol compared with 62.0% (with 800 mcg vaginal misoprostol), 68.5% (with 800 mcg oral misoprostol), 60.0% (with 800 mcg SL misoprostol), and 50.9% (with 1,600 mcg buccal misoprostol alone). The frequency of vomiting ranged from 20.0% to 47.6% and

diarrhea from 36.1% to 61.2% with 200 mg oral mifepristone and 800 mcg buccal misoprostol compared with 31.9% and 23.9% (800 mcg vaginal misoprostol), 43.5% and 38.7% (800 mcg oral misoprostol), 33.3% and 37.8% (800 mcg SL misoprostol), and 39.9% and 83.9% (1,600 mcg buccal misoprostol alone).

The proportions of patients with individual TEAEs were similar between treatment arms in the included trials, with the possible exception of misoprostol administered by the SL route in Study 4 (e.g., higher proportions of patients in the SL group reported nausea, vomiting, and fever/chills than in the buccal group) and the misoprostol-alone group in Study 5 (e.g., diarrhea was reported by 83.9% of patients in the misoprostol-alone group compared with 61.2% in the mifepristone and misoprostol group).

The primary outcome in Study 4 was the proportion of patients with fever; 22.2% of patients in the 800 mcg buccal misoprostol group reported fever greater than 38°C compared with 37.8% of patients in the 800 mcg SL group, and the difference was not statistically significant. The incidence of fever or fever/chills was reported differently in the trials. Fever alone was reported as a TEAE in Studies 1, 4, and 5, whereas combined fever/chills was reported in Studies 2 and 3, and chills/shivering and chills alone were reported in Studies 4 and 5, respectively. In Studies 1, 4, and 5, the proportion of patients with fever reported alone ranged from 22.2% to 42.1% with 200 mg oral mifepristone and 800 mcg buccal misoprostol compared with 50.7% (with 800 mcg misoprostol vaginally), 37.8% (with 800 mcg misoprostol SL), and 33.0% (with 1,600 mcg misoprostol alone). In Studies 2, 3, and 4, fever/chills ranged from 30.6% to 55.6% with 200 mg oral mifepristone and 800 mcg buccal misoprostol) compared with 47.6% (800 mcg vaginal misoprostol), 91.1% (800 mcg SL misoprostol), and 38.5% (1,600 mcg buccal misoprostol alone).

3.7.2 Serious Adverse Events

The proportion of patients with SAEs was reported only in Study 3 (Table 8). In total, 11 patients (11.1%) experienced SAEs which primarily included heavy bleeding, fainting, and lower abdominal pain requiring hospitalization and D&C. One patient had tachycardia and respiratory difficulties but was hospitalized for D&C for problematic bleeding.

3.7.3 Withdrawal Due to Adverse Events

There were no WDAEs reported in any of the included trials.

3.7.4 Mortality

There were no deaths reported in any of the included trials.

3.7.5 Notable Harms

Notable harms, as identified in consultation with the clinical expert, included gastrointestinal-related adverse events, reproductive system–related adverse events, QT prolongation, and embryotoxicity (Table 8). Of these, specific data were available only from Study 4, in which lower abdominal pain was reported as a separate TEAE by almost all women (i.e., 97.8% in the buccal misoprostol group and 100.0% in the SL misoprostol group). In Study 1, endometritis was reported in four patients (1.9%) in the vaginal misoprostol group compared with no patients in the buccal misoprostol group.

TABLE 8: HARMS

Characteristic	Study 1		Study 2[a]		Study 3	Study 4[b]		Study 5	
	Miso 800 mcg Buccal N = 216	Miso 800 mcg Vaginal N = 213	Miso 800 mcg Buccal N = 414	Miso 800 mcg Oral N = 416	Miso 800 mcg Buccal N = 969	Miso 800 mcg Buccal N = 45	Miso 800 mcg SL N = 45	Miso 800 mcg Buccal N = 209	Miso 1,600 mcg Buccal N = 218
No. of deaths, n (%)	0	0	0	0	0	0	0	0	0
Pts with ≥ 1 AE, n (%)	NR	NR	393 (94.9)	405 (97.3)	858 (88.5)	NR	NR	NR	NR
Most common AEs, n (%)									
Nausea	150 (69.4)	132 (62.0)	311 (75.1)	285 (68.5)	331 (34.2)	21 (46.7)	27 (60.0)	96 (45.9)	111 (50.9)
Weakness	118 (54.6)	108 (50.7)	240 (58.0)	223 (53.6)	203 (20.9)	NR	NR	NR	NR
Headache	94 (43.5)	104 (48.8)	179 (41.1)	160 (38.5)	135 (13.9)	8 (17.8)	9 (20.0)	NR	NR
Fever[c]	91 (42.1)	108 (50.7)	NR	NR	NR	10 (22.2)	17 (37.8)	59 (28.2)	72 (33.0)
Fever/chills[c]	NR	NR	197 (47.6)	150 (36.1)	439 (45.3)	25 (55.6)	41 (91.1)	64 (30.6)	84 (38.5)
Dizziness	88 (40.7)	90 (42.3)	163 (39.4)	156 (37.5)	127 (13.1)	14 (31.1)	11 (24.4)	NR	NR
Vomiting	80 (37.0)	68 (31.9)	197 (47.6)	181 (43.5)	256 (26.4)	9 (20.0)	15 (33.3)	79 (37.8)	87 (39.9)
Diarrhea	78 (36.1)	51 (23.9)	178 (43.0)	161 (38.7)	577 (59.5)	14 (31.1)	17 (37.8)	128 (61.2)	183 (83.9)
Pts with ≥ 1 SAE, n (%)	0	0	NR	NR	11 (1.1)[d]	NR	NR	NR	NR
Pts with ≥ 1 WDAE, n (%)	0	0	0	0	0	0	0	0	0

Characteristic	Study 1		Study 2[a]		Study 3	Study 4[b]		Study 5	
	Miso 800 mcg Buccal N = 216	Miso 800 mcg Vaginal N = 213	Miso 800 mcg Buccal N = 414	Miso 800 mcg Oral N = 416	Miso 800 mcg Buccal N = 969	Miso 800 mcg Buccal N = 45	Miso 800 mcg SL N = 45	Miso 800 mcg Buccal N = 209	Miso 1,600 mcg Buccal N = 218
Notable AEs, n (%)									
Lower abdominal pain	NR	NR	NR	NR	NR	44 (97.8)	45 (100)	NR	NR
Endometritis	0	4 (1.9)	NR	NR	NR	NR	NR	NR	NR

AE = adverse event; Miso = misoprostol; pt = patient; NR = not reported; SAE = serious adverse event; SL = sublingual; WDAE = withdrawal due to adverse event.
[a] Results are AEs reported in patient's diary.
[b] In Study 4, AEs are reported within 4 hours of buccal and SL misoprostol administration.
[c] Fever alone was reported as an AE in Studies 1, 4, and 5, combined fever/chills was reported in Study 2, and chills alone or chills/shivering alone was reported in Studies 4 and 5.
[d] SAEs included primarily heavy bleeding, fainting, and lower abdominal pain requiring hospitalization for D&C. One patient had tachycardia and respiratory difficulties but was hospitalized for D&C for problematic bleeding.
Source: Middleton et al., 2005,[6] clinical study report[13], Winikoff et al., 2008[7], clinical study report[14], Pena et al., 2014,[5] clinical study report,[15] Chai et al., 2013,[8] Blum et al., 2012.[9]

4. DISCUSSION

4.1 Summary of Available Evidence

Five prospective trials met the selection criteria for inclusion in the systematic review. Three open-label trials were considered pivotal by Health Canada: Study 1 (N = 442), Study 2 (N = 966), and Study 3 (N = 1,000). As well, two double-blind trials were identified from the clinical literature search: Study 4 (N = 90) and Study 5 (N = 441). Three trials (Study 1, Study 2, and Study 4) were randomized, parallel-group comparisons of different ROAs of misoprostol (i.e., oral, vaginal, and SL) with buccal misoprostol, all following a single oral dose of mifepristone. Study 5 was a randomized comparison of oral mifepristone followed by buccal misoprostol versus buccal misoprostol alone. Study 3 was a nonrandomized, single-arm trial of the Health Canada–approved mifepristone and misoprostol regimen. All trials enrolled women of child-bearing age (14 years and older) who were voluntarily seeking medical abortion with gestational age of up to 56 to 63 days since LMP. In all the trials, a subpopulation of women with pregnancies ≤ 49 days based on LMP (as per the Health Canada–approved regimen for Mifegymiso) could be identified.

Key limitations of the available evidence are the lack of comparison with surgical abortion or with methotrexate and misoprostol (which constitute the standard of care for abortion in Canada), uncertainty whether the subgroups reported in the trials were pre-specified, lack of stratification by gestational age, and lack of control or adjustments of secondary outcomes for multiplicity.

4.2 Interpretation of Results

4.2.1 Efficacy

Across all of the five included trials, success rates for medical abortion (defined as complete abortion without surgical intervention at any time) with the regimen of 200 mg oral mifepristone and 800 mcg buccal misoprostol were similar in the overall study populations (92.9% to 97.3%) and in women with gestational age ≤ 49 days (95.2% to 100.0%). There were no statistically significant differences in success rates when 200 mg oral mifepristone and 800 mcg buccal misoprostol was compared with 200 mg oral mifepristone and 800 mcg misoprostol administered by the vaginal or SL route; however, success rates with 200 mg oral mifepristone and 800 mcg buccal misoprostol were statistically significantly higher than with 200 mg oral mifepristone and 800 mcg misoprostol administered orally. The superiority of buccal over oral administration of misoprostol has been attributed to pharmacokinetic differences between the respective ROAs, as oral administration of misoprostol results in a rapid peak in serum levels, which increases uterine tone but not sustained uterine contractions, whereas buccal (and vaginal) administration results in regular and sustained uterine contractility.[7,14]

The 200 mg oral mifepristone and 800 mcg buccal misoprostol regimen also resulted in a statistically significantly higher success rate when compared with 1,600 mcg misoprostol alone (i.e., two doses of 800 mcg misoprostol given three hours apart). These results are consistent with recommendations in the 2016 SOGC guideline on medical abortion, which states that, although misoprostol-alone regimens have been used in Canada, they usually require repeated doses and are not as effective as other regimens.[1] Of note, an earlier publication by the same researchers in Study 5 reported superior efficacy of 200 mg oral mifepristone and 800 mcg buccal misoprostol compared with two doses of 800 mcg buccal misoprostol administered 24 hours apart.[10] The study was terminated early after an interim analysis because of the high failure rate in women randomized to misoprostol alone (i.e., ongoing pregnancy was documented for 16.6% of women taking misoprostol alone).[10] Results following a second

dose of misoprostol were reported only in Study 2, in which success rates improved following use of a second dose of misoprostol.

The systematic review summarized in Appendix 5 compared medical and surgical abortion.[11] No statistically significant difference in the rate of failure was found when the combination of mifepristone and prostaglandin was compared with surgical abortion by vacuum aspiration (one trial, OR 2.12; 95%CI, 0.37 to 12.06). As surgical abortion is the primary method of abortion in Canada, the lack of a direct comparison of the Mifegymiso regimen with surgical abortion represents an important evidence gap.

There is also a lack of direct evidence comparing the 200 mg oral mifepristone and 800 mcg buccal misoprostol regimen with methotrexate and misoprostol, which is the current standard of care for medical abortion in Canada. The effectiveness of 50 mg oral or intramuscular methotrexate and 800 mcg vaginal misoprostol in women with pregnancies of gestational age ≤ 56 to 63 days is reported to range between 81.7% to 98%.[1] A systematic review[25] (Appendix 5) reported only that the ROA of methotrexate (intramuscular versus oral) in the combined methotrexate and prostaglandin regimen showed no statistically significant difference (RR 2.04; 95%CI, 0.51 to 8.07), nor did the timing of the prostaglandin component. The systematic review made no direct comparisons between the methotrexate and prostaglandin regimen and the mifepristone and prostaglandin regimen. According to the clinical expert, the use of methotrexate and misoprostol can also take up to four weeks to be effective, which is a major disadvantage with this regimen. The methotrexate and misoprostol regimen is also less effective as gestational age advances, and there is serious known risk of embryotoxicity or teratogenic effects associated with the use of methotrexate.[1,12]

Success rates with Mifegymiso in women with gestational age ≤ 49 days were consistent with those in the overall populations in all the trials, and in some cases were reported to be slightly higher (i.e., 95.2% to 100.0%). According to the 2016 SOGC guideline, medical abortion with oral mifepristone 200 mg and buccal, vagina, or SL misoprostol 800 mcg is considered as effective and safe as surgical abortion before 49 days following the LMP.[1] It is important that gestational age fall within the limits for medical abortion, as effectiveness of medical regimens decreases as gestational age increases, and underestimation of gestational age could result in a woman receiving a treatment that may be inappropriate for medical abortion.[1] The rates of ongoing pregnancies were compared by gestational age in Studies 2 and 5. Although statistical comparisons were not made between gestational age groups in the included trials, the proportion of women with ongoing pregnancies appeared to be higher in women with advanced gestational age (e.g., in Study 2, 1.0% and 3.5% of women in the overall study population compared with 1.7% and 7.9% of women with pregnancies of gestational age 57 to 63 days had ongoing pregnancies following buccal and oral misoprostol, respectively).

Rates of complications (e.g., bleeding, infection, pain), as identified in the review protocol, were not consistently reported in the included trials. Rather, in Studies 1, 2, and 3, specific complications in individual patients (e.g., persistent vomiting, pain, heavy bleeding, pelvic tenderness/endometritis, and suspected infections) were reported in the text of the publications.[5-7,13-15] Two patients (one each in Studies 1 and 3) required a blood transfusion due to heavy bleeding.[5,6,13,15] In Studies 2, 3, and 5, upon study completion, women were questioned regarding the amount of bleeding or pain they experienced relative to their expectations. In Studies 1 and 2, for women with pregnancies of gestational age ≤ 49 days, the mean number of days of bleeding was approximately two days of heavy bleeding, four to five days of normal bleeding, and four to five days of spotting, or approximately 10 to 11 days of total bleeding time. In Study 4, although more than two-thirds of women in each treatment group reported

bleeding on day 15, mean hemoglobin levels in these women did not appear to change when measured at approximately six weeks (day 43) after the procedure.

In general, overall satisfaction with the 200 mg oral mifepristone and 800 mcg buccal/vaginal/oral/SL misoprostol regimens was high across the trials that reported this outcome (Appendix 4). According to the 2016 SOGC guideline and the clinical expert, women who can choose their method of abortion have higher satisfaction rates.[1] A primary complaint associated with buccal administration of misoprostol in Studies 1 and 2 was the bitter and chalky taste of misoprostol.

There were no results reported in the included trials for other efficacy outcomes identified in the review protocol (HRQoL, psychiatric/psychological morbidity, and health care resource utilization). Of these, information on HRQoL would have been particularly valuable. As stated earlier in the report, key features of medical abortion compared with surgical abortion are the avoidance of surgery, longer procedure (days or weeks compared with minutes), usually more pain, heavier bleeding, more physician visits for assessment, medication administration, follow-up, medication costs that may need to be borne by the patient versus no cost for surgery if a patient has provincial insurance, and increased anonymity,[1] all of would be expected to significantly affect patients' HRQoL. The lack of information on health care resource utilization following medical abortion compared with surgical abortion is an important evidence gap, especially since medical abortion has the potential to reduce health-system costs by avoiding surgery, facilitate the provision of abortion care, and mitigate some of the logistical challenges reported by rural and hospital-based providers.[1]

4.2.2 Harms

Overall, TEAEs were experienced by the majority of the women in the trials and were consistent with the known effects of prostaglandins (e.g., nausea, vomiting, diarrhea, dizziness, headache, and thermoregulatory symptoms such as fever and chills).[1] There were no deaths reported in any of the included trials, and SAEs were reported only in Study 3. In most of the included trials, the proportion of patients reporting TEAEs was similar between treatment arms, with the possible exception of more TEAEs following misoprostol administration by the SL route in Study 4 and in the misoprostol-alone group in Study 5. In Study 4, more patients in the misoprostol SL group reported nausea, vomiting, and fever/chills compared with the buccal misoprostol group. Of these, most notable is fever, which was reported in 91.9% of patients receiving SL misoprostol and 55.6% of those receiving buccal misoprostol. In the misoprostol-alone group in Study 5, more patients reported diarrhea (83.9%) compared with mifepristone and misoprostol (55.6%), which may be owing to the higher dose of misoprostol administered.

4.3 Other Considerations

The manufacturer has advised that an SNDS is under review by Health Canada to extend the indication for Mifegymiso to gestational age of up to 63 days and to modify the distribution process in Canada.

4.4 Potential Place in Therapy[1]

Less than 5% of abortions in Canada are medical abortions, compared with more than 50% in countries such as England, where mifepristone has been available for more than 20 years.[1,26] Currently, medical abortions in Canada are performed with off-label use of methotrexate and misoprostol. While no direct

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

comparative evidence exists, and there are major limitations to comparing raw data between trials, the methotrexate and misoprostol combination appears to have lower reported efficacy rates than mifepristone for termination of pregnancy, and the process can take up to four weeks to complete. Mifepristone in combination with misoprostol is the gold standard for medical abortion, and, in fact, both drugs are on the WHO's Essential Medicines List. Mifepristone has been used since 1988 and is currently approved in more than 60 countries for medical abortion, thereby establishing a long history of efficacy, safety, and acceptability for both patients and health care professionals.[1,27]

Mifegymiso has several advantages over the off-label drugs currently used in Canada for medical abortion. First, it is the only drug approved by Health Canada for medical abortion. It is also effective in a shorter length of time. Having access to an approved, effective, acceptable method for medical abortion could decrease the number of surgical abortions performed in Canada, opening up operating room time for other surgery. In addition, since provision of medical abortion does not require specialized surgical training, Mifegymiso could be prescribed by family physicians. This, in turn, could increase abortion access in rural and remote areas, where women currently have to travel long distances to access abortion services.

Mifegymiso is approved by Health Canada for use in pregnancies up to 49 days' gestation based on ultrasonography. Early dating ultrasonographic examinations are usually performed for both medical and surgical abortions, so no additional testing would be required to identify this population. However, based on the 2016 SOGC guideline, Mifegymiso can be used to terminate pregnancies up to 70 days' gestation, beyond the current Health Canada–approved indication.[1] This is also supported by Society of Family Planning guidelines.[28] Use of Mifegymiso will permit women to obtain the abortion method of their choice, be it medical or surgical, and could improve access to abortion services across Canada.

5. CONCLUSIONS

In five prospective trials, the regimen of 200 mg oral mifepristone followed by 800 mcg buccal misoprostol 24 to 72 hours later was effective at inducing complete abortion without surgical intervention at any time in women of child-bearing age voluntarily seeking medical abortion for pregnancies of gestational age up to 56 to 63 days. Rates of complete abortion with this regimen in women with pregnancies of gestational age ≤ 49 days were consistent with those in the overall study populations in all of the trials. The regimen was also shown to be superior to 200 mg oral mifepristone and 800 mcg oral misoprostol and to 1,600 mcg misoprostol alone. In general, most patients were satisfied with the regimen for medical abortion. Rates of complications were low across all trials. There were no deaths or WDAEs reported in any of the included trials, and SAEs were reported in only one trial. While TEAEs were experienced by the majority of the women in the trials, they were consistent with the known effects of prostaglandins (e.g., nausea, vomiting, diarrhea, and thermoregulatory symptoms). In most of the included trials, the proportion of patients reporting TEAEs was similar between treatment arms, with the possible exception of more nausea, vomiting, and fever/chills with SL misoprostol and diarrhea with misoprostol alone (which was administered at twice the dose used in the other trials). An important limitation is the lack of evidence directly comparing the Mifegymiso regimen with surgical abortion or with methotrexate and misoprostol, which constitute the standard of care for abortion in Canada.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

No patient input was received in response to the Call for Patient Input for Mifegymiso by CADTH.

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 9 2016
Alerts:	Bi-weekly search updates until March 15 2017
Study Types:	Systematic reviews; meta-analyses; network meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials;
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
#	Searches	
1	Mifegymiso*.ti,ab,kf,kw,ot,hw,rn,nm.	2
2	Mifepristone/	17152
3	(mifepriston* or Korlym* or Mifeprex* or Abortom* or Apano* or Mifegyn* or Mifehin* or Mifestad* or Mifolian* or Mifotab* or MTPill* or Nopreg or "Si Mi An" or Zacafemyl*).ti,ab,kf,ot,hw,rn,nm.	18274
4	(ZK-98296 or ZK 98296 or ZK98296 or corlux* or corluxin* or korlym* or lunarette* or mifegest* or mifegyne* or mifeprex* or pictovir* or "ru 38 486" or "ru 38486" or "ru 486" or r38486 or r-38486 or "ru38486" or ru486 or "vgx 410" or "vgx 410c" or "vgx410" or "vgx410c").ti,ab,kf,ot,hw,rn,nm.	9649
5	(320T6RNW1F or 84371-65-3 or "ru 38 486" or "ru 38486" or "ru 486" or r38486 or r-38486 or "ru38486" or ru486 or "vgx 410" or "vgx 410c" or "vgx410" or "vgx410c").rn,nm.	15981
6	or/2-5	19965
7	6 use ppez	7808
8	Misoprostol/	14173
9	(Misoprost* or Cytotec* or Aboprost* or Alsoben* or Alumbra* or Asotec* or Chromalux* or Cyprostol* or Cytil* or cyprostol* or Cytofine* or Cytolog* or Cytotec* or Gastrul* or gastotec* or glefos* or Gymiso* or hemoprostol* or Herwont* or Invitec* or Isovent* or isprelor* or Mipros or Misel or Miso-Fem or misofar or Misoclear or Misodel or MisoOne or Misopa or misopress* or Misotrol* or mispregnol* or Mizoprost* or Mizotab* or Mysodelle* or Noprostol* or Oxaprost* or Prosomed* or Topogyne* or U-Miso or sc 29333 or sc 30249 or sc29333 or sc30249 or xp 16j or xp16j).ti,ab,kf,ot,hw,rn,nm.	586478
10	(sc 29333 or sc 30249 or sc29333 or sc30249 or xp 16j or xp16j or 59122-46-2 or 59122-48-4 or HSDB-3573).rn,nm.	9472
11	or/8-10	586478
12	11 use ppez	110088
13	7 and 12	906
14	*Mifepristone/	6847
15	(mifepriston* or Korlym* or Mifeprex* or Abortom* or Apano* or Mifegyn* or Mifehin* or Mifestad* or Mifolian* or Mifotab* or MTPill* or Nopreg or "Si Mi An" or Zacafemyl*).ti,ab,kw.	7203
16	(ZK-98296 or ZK 98296 or ZK98296 or corlux* or corluxin* or korlym* or lunarette* or mifegest* or mifegyne* or mifeprex* or pictovir* or "ru 38 486" or "ru 38486" or "ru 486" or r38486 or r-38486 or "ru38486" or ru486 or "vgx 410" or "vgx 410c" or "vgx410" or "vgx410c").ti,ab,kw.	9629
17	or/14-16	15938
18	17 use oemezd	8891
19	*Misoprostol/	7427
20	(Misoprost* or Cytotec* or Aboprost* or Alsoben* or Alumbra* or Asotec* or Chromalux* or Cyprostol* or Cytil* or cyprostol* or Cytofine* or Cytolog* or Cytotec* or Gastrul* or gastotec* or glefos* or Gymiso* or hemoprostol* or Herwont* or Invitec* or Isovent* or isprelor* or Mipros or Misel or Miso-Fem or misofar or Misoclear or Misodel or MisoOne or Misopa or misopress* or Misotrol* or mispregnol* or Mizoprost* or Mizotab* or Mysodelle* or Noprostol* or Oxaprost* or Prosomed* or Topogyne* or U-Miso or sc 29333 or sc 30249	219695

MULTI-DATABASE STRATEGY		
#	Searches	
	or sc29333 or sc30249 or xp 16j or xp16j).ti,ab,kw.	
21	19 or 20	220612
22	21 use oemezd	121232
23	18 and 22	1178
24	conference abstract.pt.	2376329
25	23 not 24	974
26	13 or 25	1880
27	1 or 26	1880
28	remove duplicates from 27	1130
29	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.	521984
30	Randomized Controlled Trial/	895431
31	exp Randomized Controlled Trials as Topic/	236914
32	"Randomized Controlled Trial (topic)"/	123825
33	Controlled Clinical Trial/	540928
34	exp Controlled Clinical Trials as Topic/	248014
35	"Controlled Clinical Trial (topic)"/	10414
36	Randomization/	172761
37	Random Allocation/	168895
38	Double-Blind Method/	254453
39	Double-Blind Procedure/	137638
40	Double-Blind Studies/	237250
41	Single-Blind Method/	48581
42	Single Blind Procedure/	26969
43	Single-Blind Studies/	50031
44	Placebos/	300163
45	Placebo/	325952
46	Control Groups/	261841
47	Control Group/	261841
48	(random* or sham or placebo*).ti,ab,hw,kf,kw.	2801568
49	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	454925
50	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1367
51	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.	936333
52	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	77246
53	allocated.ti,ab,hw.	111761
54	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	69179
55	or/29-54	3621024
56	meta-analysis.pt.	75231

MULTI-DATABASE STRATEGY		
#	Searches	
57	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	370225
58	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	236629
59	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.	16327
60	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	40592
61	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	40210
62	(handsearch* or hand search*).ti,ab,kf,kw.	15791
63	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	42731
64	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.	16733
65	(meta regression* or metaregression*).ti,ab,kf,kw.	10942
66	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	488356
67	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	318400
68	(cochrane or (health adj2 technology assessment) or evidence report).jw.	39636
69	(meta-analysis or systematic review).md.	0
70	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.	23202
71	(outcomes research or relative effectiveness).ti,ab,kf,kw.	17323
72	((indirect or indirect treatment or mixed treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.	5958
73	(network* adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.	3722
74	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.	416
75	umbrella review*.ti,ab,kf,kw.	141
76	nma.ti,ab,kf,kw.	3283
77	(Multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	31
78	(Multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	26
79	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	24
80	MPES.ti,ab,kw,kf.	480
81	or/56-80	764998
82	55 or 81	4089090

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	To November 9 2016
Keywords:	Mifegymiso, Mifepristone, Misoprostol
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health technology assessment agencies
- Health economics
- Clinical practice guidelines
- Drug and device regulatory approvals
- Advisories and warnings
- Drug class reviews
- Databases (free)
- Internet search.

APPENDIX 2: EXCLUDED STUDIES

Reference	Reason for Exclusion
Dahiya K, Ahuja K, Dhingra A, Duhan N, Nanda S. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. Arch Gynecol Obstet. 2012 Apr;285(4):1055-8. [29]	Incorrect patient population (cannot identify gestation ≤ 49 days from LMP)
Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol. 2008 Dec;112(6):1303-10.[7]	Duplicate publication (identified as Dzuba et al., 2008)
Chawdhary R, Rana A, Pradhan N. Mifepristone plus vaginal misoprostol vs vaginal misoprostol alone for medical abortion in gestation 63 days or less in Nepalese women: a quasi-randomized controlled trial. J Obstet Gynaecol Res. 2009 Feb;35(1):78-85. [30]	Incorrect ROA (vaginal misoprostol)
Mittal S, Agarwal S, Kumar S, Batra A. Comparison or oral versus vaginal misoprostol & continued use of misoprostol after mifepristone for early medical abortion. Indian J Med Res. 2005 Aug;122(2):132-6.[31]	Incorrect ROA (vaginal or oral misoprostol)
Tang OS, Chan CC, Ng EH, Lee SW, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. Hum Reprod. 2003 Nov;18(11):2315-8.[32]	Incorrect ROA (vaginal or SL misoprostol)
Von HH, Honkanen H, Piaggio G, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, et al. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy. BJOG. 2003 Sep;110(9):808-18.[33]	Incorrect ROA (vaginal or oral misoprostol)
Jain JK, Dutton C, Harwood B, Meckstroth KR, Mishell DR, Jr. A prospective randomized, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. Hum Reprod. 2002 Jun;17(6):1477-82.[34]	Incorrect ROA (vaginal misoprostol)
Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. Contraception. 2001 Aug;64(2):81-5.[35]	Incorrect ROA (vaginal or oral misoprostol)

LMP = last menstrual period; ROA = route of administration; SL = sublingual.

APPENDIX 3: DETAILED OUTCOME DATA

TABLE 9: STUDY 1 — PREGNANCY OUTCOME BY TREATMENT GROUP

	Study 1		
	Miso 800 mcg Buccal N = 216	Miso 800 mcg Vaginal N = 213	Chi-square; *P* value
Success, n (%)	205 (94.9)	199 (93.4)	Chi-square = 0.43; *P* = 0.51
Gestational age, n/N (%)			
≤49 days[a]	139/146 (95.2)	NR	NR
Failures, n (%)	11 (5.1)	14 (6.6)	NR
Reason for surgical intervention:			
Continuing pregnancy	2 (0.9)	4 (1.9)	NR
Incomplete and bleeding	9 (4.2)	8 (3.8)	NR
Abdominal pain[b]	0	1 (0.5)	NR
Hyperemesis	0	1 (0.5)	NR

Miso = misoprostol; NR = not reported.
[a] Results reported for mifepristone and buccal misoprostol group for Study 1 from Mifegymiso product monograph.[4]
[b] Due to concern about retained products and infection.
Source: Middleton et al., 2005,[6] clinical study report,[13] Mifegymiso product monograph.[4]

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TABLE 10: STUDY 2 — PREGNANCY OUTCOME BY TREATMENT GROUP

	Study 2		
	Miso 800 mcg Buccal N = 421	Miso 800 mcg Oral N = 426	RR [95% CI]
Success, n (%) [95% CI]	405 (96.2)[a] [93.9 to 97.8]	389 (91.3)[a] [88.2 to 93.8]	0.95 [0.92 to 0.98]
Gestational age, n/N (%)			
≤ 42 days	75/76 (98.7) [92.9 to 100.0]	90/92 (97.8) [92.4 to 99.7]	0.99 [0.93 to 1.03]
43 to 49 days	132/137 (96.4) [91.7 to 98.8]	107/113 (94.7) [88.8 to 98.0]	0.93 [0.86 to 1.00]
50 to 56 days	89/93 (95.7)[b] [89.4 to 98.8]	95/107 (88.8)[b] [81.2 to 94.1]	0.69 [0.56 to 1.04]
57 to 63 days	109/115 (94.8)[a] [89.0 to 98.1]	97/114 (85.1)[a] [77.2 to 91.1]	0.90 [0.82 to 0.98]
Gestational age, n/N (%)			
< 49 days[c]	208/214 (97.3)	NR	NR
Failures, n (%)	16 (3.8)[a] [2.2 to 6.1]	37 (8.7)[a] [6.2 to 11.8]	2.29 [1.29 to 4.04]
Reason for surgical intervention:	4 (1.0)[a] [0.3 to 2.4]	15 (3.5)[a] [2.0 to 5.7]	3.71 [1.24 to 11.07]
Ongoing pregnancy, n (%)	1/76 (1.3) [0.0 to 7.1]	2/92 (2.2) [0.3 to 7.6]	1.65 [0.15 to 17.87]
Gestational age, n/N (%) ≤ 42 days	1/137 (0.7) [0.0 to 4.0] 0/93 (0.0) [0.0 to 3.2]	1/113 (0.9) [0.0 to 4.8] 3/107 (2.8) [0.6 to 8.0]	1.21 [0.08 to 19.17] -

	Study 2		
	Miso 800 mcg Buccal N = 421	Miso 800 mcg Oral N = 426	RR [95% CI]
43 to 49 days	2/115 (1.7)[a] [0.2 to 6.1]	9/114 (7.9)[a] [3.7 to 14.5]	4.54 [1.0 to 20.55]
50 to 56 days	8 (1.9) [0.8 to 3.7]	11 (2.6) [1.3 to 4.6]	1.36 [0.55 to 3.34]
57 to 63 days	4 (1.0) [0.3 to 2.4]	10 (2.3) [1.1 to 4.3]	2.47 [0.78 to 7.82]
Medically necessary, n (%)	0 (0.0) [0.0 to 0.7]	1 (0.2) [0.0 to 1.3]	-
Persistent sac, n (%)			
Patient request, n (%)			

CI = confidence interval; Miso = misoprostol; NR = not reported; RR = relative risk.
Note: Success was defined as complete abortion without surgical intervention at any time. For success, a RR < 1 means the event is less likely to occur in the comparator group than the Miso 800 mcg buccal group. For failures, a RR > 1 means the event is more likely to occur in the comparator group than the Miso 800 mcg buccal group.
[a] $P < 0.048$ (oral versus buccal groups).
[b] $P < 0.10$ (oral versus buccal groups).
[c] Results reported for mifepristone and buccal misoprostol group for Study 2 from Mifegymiso product monograph.[4]
Source: Winikoff et al., 2008,[7] clinical study report,[14] Mifegymiso product monograph.[4]

TABLE 11: STUDY 3 — PREGNANCY OUTCOME

	Study 3
	N = 971
Success, n (%)	945 (97.3)
Gestational age, n/N (%)	
≤ 49 days	540/551 (98.0)
50 to 56 days	239/247 (96.8)
57 to 63 days	164/171 (95.9)
> 64 days	2/2 (100)
Gravidity, n /N (%)	
Primigravida	342/352 (97.2)
Multigravida	603/619 (97.4)
Failures, n (%)	26 (2.7)
Gestational age, n/N (%)	
≤ 49 days	11/551 (2.0)
50 to 56 days	8/247 (3.2)
57 to 63 days	7/171 (4.1)
> 64 days	-
Reason for surgical intervention:	
Ongoing pregnancy, n (%)	6 (0.6)
Gestational age, n/N (%)	
≤ 49 days	3/551 (0.6)
50 to 56 days	1/247 (0.4)
57 to 63 days	2/171 (1.2)
> 64 days	-
Persistent sac, n (%)	2 (0.2)
Gestational age, n/N (%)	
≤ 49 days	-
50 to 56 days	1/247 (0.4)
57 to 63 days	1/171 (0.6)

	Study 3 N = 971
> 64 days	-
Bleeding, n (%)	16 (1.7)
Gestational age, n/N (%)	
≤ 49 days	6/551 (1.1)
50 to 56 days	6/247 (2.4)
57 to 63 days	4/171 (2.3)
> 64 days	-
Other[a], n (%)	2 (0.2)
Gestational age, n/N (%)	
≤ 49 days	2/551 (0.4)
50 to 56 days	-
57 to 63 days	-
> 64 days	-
Gravidity, n/N (%)	
Primigravida	10/352 (2.8)
Multigravida	16/619 (2.6)

[a] Reason indicated was pain.
Source: Pena et al., 2014,[5] clinical study report.[15]

TABLE 12: STUDY 4 — PREGNANCY OUTCOME BY TREATMENT GROUP

	Study 4	
	Miso 800 mcg Buccal N = 45	Miso 800 mcg SL N = 45
Success, n (%) **[95% CI]**	43 (95.6)[a] [84.9 to 99.5][b]	44 (97.8) [88.2 to 99.9][b]
Gestational age, days, n/N (%) **< 49 days** **>49 to 63 days**	 22/22 (100.0) 21/23 (91.3)	 26/26 (100.0) 18/19 (94.7)
Failures, n (%)	0 (0)	1 (2.2)
Ongoing pregnancy, n/N (%) **< 49 days** **>49 to 63 days**	 0 (0) 0 (0)	 0/26 (0) 1/19 (5.3)
Induction to abortion interval for successful abortions, hours **Median (range)**	3.3 (1.45 to 6.9)	3.1 (0.83 to 5.2)

Miso = misoprostol; SL = sublingual.
[a] Two patients were lost to follow-up on day 43.
[b] The difference was reported to be "not statistically significant" in the publication but no *P* value was reported.
Source: Chai et al., 2013.[8]

TABLE 13: STUDY 5 — PREGNANCY OUTCOME BY TREATMENT GROUP

	Study 5			
	Miso 800 mcg Buccal N = 220[a]	Miso 1,600 mcg Buccal N = 221[b]	RR [95% CI]	*P* value
Success, n/N (%)	195/210 (92.9)	170/218 (78.0)	0.84 [0.78 to 0.91]	< 0.001
Gestational age, n/N (%)				
≤ 49 days	105/109 (96.3)	95/121 (78.5)	0.82 [0.74 to 0.90]	< 0.001
50 to 56 days	64/74 (86.5)	53/70 (75.7)	0.88 [0.75 to 1.03]	0.098
57 to 63 days	26/27 (96.3)	22/27 (81.5)	0.85 [0.70 to 1.03]	0.083
Failures, n (%)	15/210 (7.1)	48/218 (22.0)	NR	NR
Reason for surgical intervention by gestational age, days:	3/210 (1.4)	30/218 (13.8)	9.63 [2.98 to 31.09]	< 0.001
Ongoing pregnancy, n/N (%)	1/109 (0.9)	16/121 (13.2)	14.41 [1.94 to 106.89]	< 0.001
< 49 days	2/74 (2.7)	11/70 (15.7)		0.006
50 to 56 days	0/27 (0)	3/27 (11.1)	5.81 [1.34 to 25.31]	0.118
57 to 63 days			NR	
Nonviable pregnancy or gestational sac, n/N (%)	0/210 (0)	9/218 (4.1)		
<49 days	0/109 (0)	5/121 (4.1)	NR	0.038
50 to 56 days	0/74 (0)	3/70 (4.3)	NR	0.112
57 to 63 days	0/27 (0)	1/27 (3.7)	NR	0.500
Incomplete abortion, n/N (%)	7/210 (3.3)	6/218 (2.8)	NR	NR
< 49 days	2/109 (1.8)	3/121 (2.5)	NR	0.738
50 to 56 days	5/74 (6.8)	3/70 (4.3)	1.35 [0.23 to 7.94]	0.518
57 to 63 days	0 (0)	0 (0)	0.63 [0.16 to 2.56]	NA
Woman's request, n/N (%)	3/210 (1.4)	3/218 (1.4)	NR	NR
Medically indicated for Hemorrhage, n/N (%)			NR	
	2/210 (1.0)	0/218 (0)		NR

CI = confidence interval; Miso = misoprostol; NA = not applicable; NR = not reported; RR = relative risk.
Note: Success was defined as complete abortion without surgical intervention at any time. For success, a RR < 1 means the event is less likely to occur in the comparator group than the Miso 800 mcg buccal group. For failures, a RR > 1 means the event is more likely to occur in the comparator group than the Miso 800 mcg buccal group.
[a] Three patients withdrew; therefore, results are reported for 210 patients with complete data.
[b] Three patients withdrew and 7 patients were lost to follow-up; therefore, results are reported for 218 patients with complete data.
Source: Blum et al., 2012.[9]

TABLE 14: STUDY 1 — PATIENT SATISFACTION WITH THE PROCEDURE

	Study 1		
	Miso Buccal N = 213	Miso Vaginal N = 210	Chi-square; *P* value
Overall satisfaction, n (%)	196 (92.0)	199 (94.8)	Chi-square = 1.83; *P* = 0.18
Gestational age, n/N (%) **≤ 49 days** **> 49 days**	 134/143 (93.7) 61/70 (87.1)	 124/132 (93.9) 76/78 (997.4)	 Chi-square = 0.03; *P* = 0.87 Chi-square = 5.68; *P* = 0.02

Miso = misoprostol.
Note: Proportion of patients "satisfied" or "very satisfied" with the procedure based on a 5-point Likert scale ranging from "very unsatisfied" to "very satisfied."
Source: Middleton et al., 2005,[6] clinical study report.[13]

TABLE 15: STUDY 2 — PATIENT SATISFACTION AND EXPERIENCE WITH THE PROCEDURE

	Study 2	
n (%)	Miso buccal, N = 415	Miso oral, N = 420
Overall satisfaction	378 (91.1)	389 (92.6)
Procedure not/slightly difficult	292 (70.4)	299 (71.2)
Amount of bleeding **Less than expected** **Same as expected** **More than expected**	 120 (28.9) 181 (43.6) 124 (29.9)	 119 (28.3) 185 (44.0) 109 (26.0)
Amount of pain **Less than expected** **Same as expected** **More than expected**	 123 (29.6)[a] 161 (38.8) 124 (29.9)	 162 (38.6)[a] 144 (34.3) 108 (25.7)
Pain acceptable	269 (64.8)	287 (68.3)
AEs acceptable	296 (71.3)	321 (76.4)
Time acceptable	343 (82.7)	350 (83.3)

AE = adverse event; Miso = misoprostol.
Note: Satisfaction with the procedure means the patient responded that the procedure was either very satisfactory or satisfactory.
[a] $P < 0.05$ (oral versus buccal groups).
Source: Winikoff et al., 2008,[7] clinical study report.[14]

TABLE 16: STUDY 3 — PATIENT SATISFACTION AND EXPERIENCE WITH THE PROCEDURE

	Study 3
	N = 969
AEs, n (%) **Acceptable** **Neutral** **Unacceptable** **Don't know**	 778 (80.3) 146 (15.1) 32 (3.3) 13 (1.3)

	Study 3 N = 969
Satisfaction with treatment, n (%)	
Satisfactory	915 (94.4)
Neutral	27 (2.8)
Unsatisfactory	27 (2.8)
Level of pain, n (%)[a]	
Less than expected	255 (26.3)
As expected	261 (26.9)
More than expected	446 (46.0)
Don't know	7 (0.7)
Level of bleeding, n (%)	
Less than expected	296 (30.5)
As expected	404 (41.7)
More than expected	262 (27.0)
Don't know	7 (0.7)

AE = adverse event.
[a] Pain severity was rated using a visual 7-point Likert scale that depicted a series of faces ranging from sad to neutral to happy. Each face represented a level of pain severity, with the happiest face representing no pain and the saddest face representing the worst pain imaginable.
Source: Pena et al., 2014,[5] clinical study report.[15]

TABLE 17: STUDIES 1, 2, AND 3 — TOTAL BLEEDING TIME BY TYPE OF BLEEDING IN DAYS

Type of Bleeding	Study 1 (N = 143)	Study 2 (N = 211)	Study 3 (N = 551)
Total bleeding time, days			
Mean (SD)	NR	10.8 (3.9)	NR
Median (range)	NR	11 (0-37)	NR
Heavy bleeding, days			
Mean (SD)	2.3 (2.3)	2.0 (2.1)	NR
Median (range)	2 (0-15)	2 (0-15)	NR
Normal bleeding, days			
Mean (SD)	5.1 (2.9)	4.3 (2.8)	NR
Median (range)	5 (0-13)	4 (0-15)	NR
Spotting, days			
Mean (SD)	3.5 (2.5)	4.6 (3.2)	NR
Median (range)	3 (0-12)	4 (0-14)	NR

NR = not reported; SD = standard deviation.
Note: Results reported for the mifepristone and buccal misoprostol arms only from the Mifegymiso product monograph.[4]
Source: Mifegymiso product monograph.[4]

TABLE 18: STUDY 4 — BLEEDING CHARACTERISTICS ASSOCIATED WITH THE PROCEDURE

	Study 5	
	Miso 800 mcg Buccal N = 45	Miso 800 mcg SL N = 45
Bleeding on day 15, n (%) [95% CI]	30 (66.7) [51.1 to 80.0][a]	33 (73.3) [53.1 to 85.4][a]
Hg level (g/L), mean (SD)		
Day 1	121 (8.6)	122 (9.8)
Day 15	123 (9.7)	123 (9.7)
Day 43	123 (11.5)	124 (10.0)

CI = confidence interval; Hg = hemoglobin; Miso = misoprostol; SD = standard deviation; SL = sublingual.
[a] Difference between groups *P* = 0.49.
Source: Chai et al., 2013.[8]

TABLE 19: STUDY 5 — PATIENT SATISFACTION AND EXPERIENCE WITH THE PROCEDURE

	Study 5			
	Miso 800 mcg Buccal N = 209	Miso 1,600 mcg Buccal N = 218	RR [95% CI]	*P* value
Experience of bleeding, n/N (%)				
More than expected	70/206 (34.0)	55/206 (26.7)	0.79 [0.59 to 1.06]	0.108
Same as expected	73/206 (35.4)	62/206 (30.1)	0.85 [0.64 to 1.12]	0.248
Less than expected	63/206 (30.6)	89/206 (43.2)	1.41 [1.09 to 1.83]	0.008
Experience of pain, n/N (%)				
More than expected	65/204 (31.9)	69/208 (33.2)	1.04 [0.79 to 1.38]	0.777
Same as expected	51/204 (25.0)	47/208 (22.6)	0.90 [0.64 to 1.28]	0.567
Less than expected	88/204 (43.1)	92/208 (44.2)	1.03 [0.82 to 1.28]	0.823
Overall experience with AEs, n/N (%)	87/209 (41.6)	80/217 (36.9)	0.89 [0.70 to 1.12]	0.314
Very acceptable	114/209 (54.5)	126/217 (58.1)	NR	NR
Acceptable	2/209 (1.0)	1/217 (0.5)	NR	NR
Neutral	5/209 (2.4)	10/217 (4.6)	NR	NR
Unacceptable	1/209 (0.5)	0/217 (0)	NR	NR
Very unacceptable				
Time required for procedure, n/N%)	4/203 (21.6)	61/190 (32.1)	1.48 [1.06 to 2.07]	0.020
More than expected	54/203 (26.6)	54/190 (28.4)	1.07 [0.77 to 1.47]	0.686
Same as expected	105/203 (51.7)	75/190 (39.5)	0.76 [0.61 to 0.95]	0.015
Less than expected				
Overall characterization of the procedure, n/N (%)				
Not difficult	142/208 (68.3)	141/214 (65.9)	0.97 [0.84 to 1.10]	0.603
Slightly difficult	53/208 (25.5)	51/214 (23.8)	0.94 [0.67 to 1.31]	0.694
Moderately difficult	10/208 (4.8)	17/214 (7.9)	1.65 [0.77 to 3.52]	0.188
Very difficult	3/208 (1.4)	5/214 (2.3)	1.62 [0.39 to 6.69]	0.501

	Study 5			
	Miso 800 mcg Buccal N = 209	**Miso 1,600 mcg Buccal N = 218**	**RR [95% CI]**	***P* value**
Overall satisfaction, n (%)				
Very satisfied	91 (43.5)	71 (32.6)	0.75 [0.59 to 0.96]	0.020
Satisfied	97 (46.4)	95 (43.6)	0.94 [0.76 to 1.16]	0.556
Neutral	16 (7.7)	37 (17.0)	2.22 [1.27 to 3.86]	0.003
Unsatisfied	5 (2.4)	13 (6.0)	2.49 [0.90 to 6.87]	0.066
Very unsatisfied	0 (0)	2 (0.9)	NR	0.165
Method of abortion selected in the future, n/N (%)				
Medical	183/197 (92.9)	166/210 (79.1)	0.85 [0.79 to 0.92]	< 0.001
Surgical	14/197 (7.1)	44/210 (20.9)	2.95 [1.67 to 5.21]	< 0.001

AE = adverse event; CI = confidence interval; Miso = misoprostol; NR = not reported; RR = relative risk.
Note: Some data are missing, as not all patients responded to all questions.
Note: An RR < 1 means the event is less likely to occur in the comparator group than the Miso 800 mcg buccal group, whereas an RR > 1 means the event is more likely to occur in the comparator group than the Miso 800 mcg buccal group.
Source: Blum et al., 2012.[9]

APPENDIX 4: SUMMARY OF SYSTEMATIC REVIEWS COMPARING MEDICAL ABORTION WITH SURGICAL ABORTION

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the results of, and critically appraise, systematic reviews of medical abortion compared with surgical abortion.

Systematic reviews had to meet the following inclusion criteria:

- The population reviewed constituted pregnant women with pregnancies of less than 49 days of gestational age.
- One of the interventions included mifepristone 200 mg followed by misoprostol 800 mg.
- One of the comparators included surgical abortion, which was compared with the mifepristone and misoprostol intervention, or a medical abortion method, which was compared with the mifepristone and misoprostol intervention.
- Outcomes include success rate, bleeding, and infection rate.
- The review was published in English.

Studies were excluded if they did not meet the inclusion criteria or did not provide sufficient reporting of the methods used.

Findings

Of 349 records retrieved in the literature search, 23 records were deemed relevant after initial screening of titles and abstracts. On further screening of the full text, two systematic reviews met our inclusion criteria.[11,25]

Say et al. and Kulier et al. were both Cochrane systematic reviews. Say et al. was first published in 2002 and updated in 2009, while Kulier et al. was first published in 2004 and assessed as up-to-date in 2011. The Say et al. review aimed to evaluate medical versus surgical methods of first-trimester abortion with regard to efficacy and safety, while Kulier et al. aimed to evaluate similar outcomes with different methods of medical abortion. Both reviews' inclusion criteria allowed all known medical abortion methods as an intervention, while the comparators were restricted to surgical methods in Say et al. and to medical methods in Kulier et al. Both reviews listed outcomes that are reflective of the procedure and the research area. The authors of both reviews restricted the included studies to randomized controlled trials.

The authors of both reviews conducted a comprehensive literature search of three bibliographical databases. They also contacted expert clinicians as well as hand-searched references to complement their search strategy. The screening process and data extraction were performed by two independent reviewers, with any discrepancies addressed through consensus. Investigators processed extracted data using the Revman software. The authors conducted their data synthesis using the Mantel–Haenszel fixed-effects model.

In the systematic review by Say et al., the authors included six trials with four different comparisons; all comparisons were against vacuum aspiration, and none included dilation and curettage. The combination of 600 mg oral mifepristone and 1 mg vaginal gemeprost prostaglandin, informed by only one trial, showed no statistically significant difference in the rate of failure when compared with vacuum aspiration (odds ratio 2.12; 95% confidence interval [CI], 0.37 to 12.06). However, the duration of bleeding among patients from a pooled heterogeneous mifepristone/prostaglandin intervention was statistically significantly higher than following vacuum aspiration (two trials, mean difference 2.94 days of bleeding; 95% CI, 2.10 to 3.78). No result was available for the rate of infection. Also, no comparison included the exact mifepristone and prostaglandin combination that matches that of Mifegymiso. Detailed outcomes of the systematic review are presented in Table 5.

The systematic review conducted by Say et al. followed a clearly stated research question and inclusion and exclusion criteria. It was conducted on several bibliographical databases using a comprehensive search strategy. The screening and extraction process was well described and would ensure high accuracy.

Some of the limitations associated with the Say et al. review are the following:

- Lack of comprehensive reporting of patients' characteristics in the trials included in the review: The authors did not include an overview or an assessment of the baseline characters of patients enrolled in the trials; this reduces our ability to assess clinical heterogeneity.
- The I^2 measure is of little informative value: For any given single comparison, a maximum of two studies informed the outcome; in such situations, the I^2 is of little value. This reduces the ability to assess for statistical heterogeneity.
- Small number of included trials: This reduces the ability of the analysis to capture meaningful differences and reduces certainty in results showing no statistically significant difference, as these results may have been due to lack of power.
- The pooling of clinically heterogeneous studies with the use of the fixed-effects model: The unclear baseline characteristics of included studies, the small number of studies informing each outcome, the different regimens of mifepristone and prostaglandin combination, and the inconsistent definition of outcomes render any pooling technique, and especially the fixed-effects model, unjustifiable.

In the systematic review by Kulier et al., the authors included 58 trials with numerous comparisons, which the authors aggregated into separate categories based on (1) two different interventions, (2) same intervention but different doses, (3) same intervention but different route of administration, or (4) same intervention but different schedule of administration. Detailed results are reported in Table 21. Informed by three trials that compared varying regimens of mifepristone alone to mifepristone and prostaglandin combination, Kulier et al. demonstrated that the pooled mifepristone alone (regimen varied in each included study) was less effective than the combined varying regimens of mifepristone and prostaglandin (rate ratio [RR] 3.76; 95% CI, 2.30 to 6.15). Similarly, the results of five trials (which were not pooled together) indicated that prostaglandin alone was less effective than the combined regimen (mifepristone and prostaglandin). When considering the combined regimen methotrexate and prostaglandin, the route of methotrexate administration (intramuscular versus oral) showed no statistically significant difference (RR 2.04; 95% CI, 0.51 to 8.07), nor did the timing of the prostaglandin component. There were no direct comparisons between methotrexate and prostaglandin and mifepristone and prostaglandin.

The systematic review conducted by Kulier et al. followed a clearly stated research question and inclusion and exclusion criteria. It was conducted on several bibliographical databases using a comprehensive search strategy. The screening and extraction process was well described and would ensure high accuracy.

Some of the limitations associated with the Kulier et al. review were the following:

- Although a large number of trials were included, only a small number of trials would inform on any given intervention and comparator, thus greatly reducing the value of any information derived from the meta-analysis regarding the efficacy of an intervention, the quality of the studies, or presence of any possible publication bias.
- The I^2 measure is of little informative value in any comparison with two or fewer trials.
- The pooling of clinically heterogeneous studies with the use of the fixed-effects model: Similar to Say et al., the small number of studies informing each outcome, the different regimens of mifepristone and prostaglandin combination, and the inconsistent definition of outcomes render any pooling technique, and especially the fixed-effects model, unjustifiable.
- Although the authors planned to report on the duration of bleeding, no synthesis of the outcome was provided.

TABLE 20: SUMMARY OF FINDINGS OF SAY ET AL.[11]

Outcome	Comparison	Number of studies	Number of patients	Estimate type	Estimate (95% CI)
Rate of failure	Prostaglandin vs. vacuum aspiration[a]	2	472	OR	2.67 (1.06 to 6.75)
	600 mg mifepristone vs. vacuum aspiration	1	50	OR	3.63 (0.66 to 20.11)
	600 mg mifepristone and prostaglandin (1 mg vaginal gemeprost) vs. vacuum aspiration	1	111	OR	2.12 (0.37 to 12.06)
	50 mg methotrexate and prostaglandin (800 mg misoprostol) vs. vacuum aspiration	1	50	OR	4.57 (0.47 to 44.17)
Duration of bleeding (days until amenorrhea)	Prostaglandin (1.5 mg PGE2 methyl sulfonylamide) vs. vacuum aspiration	1	419	Mean difference	5.2 (4.98 to 5.42)
	Mifepristone and prostaglandin vs. vacuum aspiration[a]	2	424	Mean difference	2.94 (2.10 to 3.78)
	50 mg methotrexate and prostaglandin (800 mg misoprostol) vs. vacuum aspiration	1	50	Mean difference	6.0 (2.94 to 9.06)
Rate of infection	Prostaglandin (1.5 mg PGE2 methyl	1	419	OR	2.17 (0.64 to 7.33)

Outcome	Comparison	Number of studies	Number of patients	Estimate type	Estimate (95% CI)
	sulfonylamide) vs. vacuum aspiration				
	600 mg mifepristone vs. vacuum aspiration	1	50	OR	0.13 (0.01 to 2.58)

CI = confidence interval; OR = odds ratio; PGE2 = prostaglandin E2; vs. = versus.
[a] Different types of prostaglandin and different regimens of mifepristone and/or prostaglandin were pooled together.
Source: Say et al.[11]

TABLE 21: SUMMARY OF RATE OF ABORTION FAILURE IN KULIER ET AL.[25]

Comparison category	Comparison	Number of studies	Number of patients	Estimate type	Estimate (95% CI)
Mifepristone/ prostaglandin (varying types of prostaglandin): dose of mifepristone	All (high- versus low-dose mifepristone with varying types of prostaglandin)	6	6,841	RR	0.90 (0.77 to 1.05)
	600 mg vs. 200 mg (varying types of prostaglandin)	4	3,494	RR	1.07 (0.87 to 1.32)
	200 mg vs. 100 mg (gestation > 49 days) (both with 800 mcg misoprostol)	1	1,182	RR	0.89 (0.61 to 1.29)
	600 mg vs. 200 mg with gemeprost 1 mg p.v. (varying types of prostaglandin)	2	1,685	RR	1.02 (0.72 to 1.45)
	200 mg vs. 100 mg (gestation ≤ 49 days) (both with 800 mcg misoprostol)	1	941	RR	0.79 (0.47 to 1.33)
Mifepristone/ prostaglandin: dose of prostaglandin	Gemeprost 1 mg vs. 0.5 mg	2	1,034	RR	0.43 (0.31,0.59)
	Misoprostol 800 p.o. or p.v. vs. 400 p.o.	2	934	RR	0.83 (0.53 to 1.31)
Combined regimen mifepristone/ prostaglandin: type of prostaglandin	Gemeprost vs. misoprostol	2	NR	RR	0.0 (0.0 to 0.0)
	PGF2 alpha vs. misoprostol	2	NR	RR	0.0 (0.0 to 0.0)
Mifepristone/ prostaglandin (varying types of	Day 3 vs. day 1	1	1,489	RR	1.94 (1.05 to 3.58)
	Day 3 vs. day 2	1	1,521	RR	1.69 (0.95 to 3.01)
	Day 2 vs. day 1 (all)	3	3,687	RR	1.24 (0.95 to 1.63)
	Day 2 vs. day 1	1	941	RR	0.81 (0.49 to 1.36)

Comparison category	Comparison	Number of studies	Number of patients	Estimate type	Estimate (95% CI)
prostaglandin): time of prostaglandin	(gestation ≤ 49 days)				
	Day 2 vs. day 1 (> 49 days)	1	1,182	RR	1.62 (1.11 to 2.38)
	Day 2 vs. day 0	2	511	RR	0.39 (0.24 to 0.65)
	Day 1 vs. day 0 (all)	2	2,156	RR	0.65 (0.46 to 0.92)
	Day 1 vs. day 0 (≤ 49 days)	2	998	RR	0.65 (0.38 to 1.14)
	Day 1 vs. day 0 (> 49 days)	2	1,158	RR	0.66 (0.41 to 1.06)
Combined regimen mifepristone/ prostaglandin: misoprostol p.o. vs. p.v.	Combined regimen mifepristone/ prostaglandin: misoprostol p.o. vs. p.v.	2	2,814	RR	30.25 (2.24 to 4.14)
Combined regimen mifepristone/ prostaglandin: misoprostol buccal vs. p.v.	Combined regimen mifepristone/ prostaglandin: misoprostol buccal vs. p.v.	1	429	RR	0.77 (0.36 to 1.67)
Combined regimen mifepristone/ prostaglandin: misoprostol buccal vs. p.o.	All	1	847	RR	0.62 (0.40 to 0.96)
	Gestation ≤ 49 days	1	418	RR	0.72 (0.25 to 2.04)
	Gestation > 49 days	1	429	RR	0.37 (0.18 to 0.73)
Combined regimen mifepristone/ prostaglandin: misoprostol sublingual vs. p.v.	Combined regimen mifepristone/ prostaglandin: misoprostol sublingual vs. p.v.	1	224	RR	0.29 (0.06 to 1.35)
Combined regimen mifepristone/ prostaglandin: misoprostol sublingual vs. p.o.	All	1	471	RR	0.21 (0.06 to 0.72)
	Gestation ≤ 49 days	1	422	RR	0.28 (0.08 to 0.99)
	Gestation > 49 days	1	48	RR	0.09 (0.00 to 1.60)
Combined regimen mifepristone/ prostaglandin: single- vs. split-dose prostaglandin	Combined regimen 200 mg mifepristone/ 800 mcg misoprostol: single- vs. split-dose prostaglandin	1	154	RR	0.70 (0.21 to 2.39)

Comparison category	Comparison	Number of studies	Number of patients	Estimate type	Estimate (95% CI)
Combined regimen mifepristone/ prostaglandin (varying types of prostaglandin: single vs. continuous prostaglandin)	All oral vs. vaginal and continuous oral	2	1,581	RR	1.48 (1.01 to 2.16)
	All oral vs. single vaginal	2	1,578	RR	1.19 (0.83 to 1.70)
	Vaginal SC continuous oral vs. single vaginal	2	1,579	RR	0.80 (0.54 to 1.19)
	All oral vs. vaginal SC continuous oral, gestation ≤ 49 days	1	476	RR	1.17 (0.57 to 2.41)
	All oral vs. vaginal SC continuous oral, gestation > 49 days	1	1,004	RR	1.60 (1.00 to 2.57)
	All oral vs. single vaginal, gestation ≤ 49 days	1	459	RR	1.29 (0.60 to 2.74)
	All oral vs. single vaginal, gestation > 49 days	1	1,014	RR	1.12 (0.73 to 1.70)
	Vaginal SC continuous oral vs. single vaginal, gestation ≥ 49 days	1	463	RR	1.10 (0.50 to 2.40)
	Vaginal SC continuous oral vs. single vaginal, gestation > 49 days	1	1,010	RR	0.70 (0.43 to 1.13)
Mifepristone alone vs. combined regimen mifepristone/ prostaglandin (varying types of prostaglandin)	Mifepristone alone vs. combined regimen mifepristone/ prostaglandin	3	273	RR	3.76 (2.30 to 6.15)
Prostaglandin alone vs. combined regimen mifepristone/ prostaglandin (varying types of prostaglandin)	All (Including one study that compared prostaglandin to combined tamoxifen/ misoprostol)	5	678	RR	2.21 (1.70,2.87)
	All without the study comparing prostaglandin to tamoxifen/ misoprostol)	4	528	RR	2.40 (1.79 to 3.20)
	Gestation ≤ 49 days	1	155	RR	2.81 (0.79 to 10.00)
	Gestation > 49 days	1	89	RR	2.93 (0.63 to 13.76)
	With methotrexate combined regime	2	133	RR	2.92 (1.79 to 4.76)

Comparison category	Comparison	Number of studies	Number of patients	Estimate type	Estimate (95% CI)
Mifepristone alone high- vs. low-dose	Mifepristone alone high- vs. low-dose	1	101	RR	1.32 (0.74 to 2.38)
Combined regimen methotrexate/ prostaglandin (varying types of prostaglandin: timing of prostaglandin)	Misoprostol day 7 vs. day 3	1	86	RR	0.14 (0.02 to 1.10)
	Misoprostol day 5 vs. day 3	2	387	RR	0.72 (0.36 to 1.43)
	Misoprostol day 5 vs. day 4	2	394	RR	0.74 (0.37 to 1.48)
	Misoprostol day 4 vs. day 3	2	393	RR	0.97 (0.52 to 1.80)
Combined regimen methotrexate/ prostaglandin: methotrexate IM vs. p.o.	Combined regimen methotrexate/ prostaglandin: methotrexate IM vs. p.o.	1	100	RR	2.04 (0.51 to 8.07)
Combined regimen methotrexate/ prostaglandin: dose of methotrexate	60 mg vs. 50 mg (both with 600 mcg misoprostol)	1	NR	RR	0.00 (0.00 to 0.00)
	50 mg vs. 25 mg (both with 600 mcg misoprostol)	1	NR	RR	0.00 (0.00 to 0.00)
Combined regimen methotrexate/ prostaglandin: route of prostaglandin (misoprostol)	Combined regimen methotrexate/ prostaglandin: route of prostaglandin (misoprostol)	1	NR	NR	NR
Tamoxifen vs. methotrexate (combined with prostaglandin): low-dose tamoxifen (40 mg)	Tamoxifen vs. methotrexate (combined with 800 mcg misoprostol): low-dose tamoxifen (40 mg)	1	198	RR	2.04 (0.86 to 4.84)
Tamoxifen vs. methotrexate (combined with prostaglandin): high-dose tamoxifen (160 mg)	Tamoxifen vs. methotrexate (combined with 800 mcg misoprostol): high-dose tamoxifen (160 mg)	1	200	RR	1.96 (0.93 to 4.15)
Combined	Combined regimen	1	NR	NR	NR

Comparison category	Comparison	Number of studies	Number of patients	Estimate type	Estimate (95% CI)
regimen mifepristone/ prostaglandin vs. mifepristone/ prostaglandin and tamoxifen	mifepristone/ prostaglandin vs. mifepristone/ prostaglandin and tamoxifen				

CI = confidence interval; IM = intramuscular injection; NR = not reported; p.o. = per os (oral); p.v. = per vagina; OR = odds ratio; RR = rate ratio; SC = subcutaneous; vs. = versus.
Source: Kulier et al.[25]

Conclusion

In a literature search, one systematic review compared medical abortion with surgical abortion, and one compared different medical abortion methods. The results indicate that mifepristone alone was less effective than the combined regimen of mifepristone and prostaglandin. Similarly, prostaglandin alone was less effective than the combined regimen (mifepristone and prostaglandin). No comparison between mifepristone and prostaglandin, on the one hand, and methotrexate and prostaglandin, on the other hand, was available. In addition, the results did not show a statistically significant difference in the rate of failure with the combination of mifepristone and prostaglandin when compared with vacuum abortion. However, mifepristone and prostaglandin showed a statistically significantly longer duration of bleeding when compared with vacuum aspiration. Although the systematic reviews were well conducted, the results are limited by the small number of trials informing each comparison, the high clinical heterogeneity in the included studies, and the decision to pool these heterogeneous data under a fixed-effects model. Finally, the fact that neither of the systematic review included a pooled analysis of the exact mifepristone and misoprostol regimen that is provided in Mifegymiso greatly reduces the applicability of the information obtained from these systematic reviews in informing the efficacy or safety of Mifegymiso.

APPENDIX 5: SUMMARY OF POST-AUTHERIZATION ACTIVITIES AND RESTRICTIONS IMPOSED ON MIFEGYMISO BY HEALTH CANADA

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the post-authorization restrictions on Mifegymiso as outlined by Health Canada's Summary Basis of Decision.[4,36]

Findings

As part of Health Canada's market authorization of Mifegymiso, the following post-authorization activities and restrictions apply:

1. Education for Mifegymiso prescribers: Physicians wishing to prescribe Mifegymiso to their patients need to undergo a training and educational program. The program is currently available through the collaboration of the Society of Obstetricians and Gynaecologists of Canada and the College of Family Physicians of Canada.[37]
2. Restrictive Distribution and Administration Program:
    a. Only physicians who undertake the designated training may prescribe and administer Mifegymiso. These physicians need also to dispense Mifegymiso in their practice, as no pharmacy will be allowed to dispense Mifegymiso to patients. A pharmacist may dispense Mifegymiso directly to physicians once they complete the appropriate training. At this time, physicians who have not undergone the designated training cannot prescribe or administer Mifegymiso. Nurse practitioners and midwives also cannot prescribe or administer Mifegymiso; pharmacists were not mentioned as possible prescribers. Pregnant women who have decided to take Mifegymiso will need to take the first pill (mifepristone) at the clinic; the subsequent pills (misoprostol) can be taken at home.
    b. Physicians and pharmacists who have completed the training need to register as providers of Mifegymiso to be able to prescribe and administer the intervention; registration is completed by signing a Prescribers' Agreement and faxing the completed agreement to Celopharma. Celopharma then confirms their accreditation status and provides a copy to a third-party logistics partner. Once this is done, Mifegymiso can then be distributed to the trained physician's clinic or to the affiliated hospital.
    c. Linepharma International Limited is the manufacturer of Mifegymiso. It provides Mifegymiso to Celopharma, the Canadian distributor (third-party logistics partner). It can provide the drug directly to a certified physician or to a wholesaler. The wholesaler then can provide the drug to a hospital affiliated with a certified physician, or to a retail pharmacy if the pharmacist has completed accreditation through the Canadian Pharmacists Association. The pharmacist cannot dispense to the patient, but may dispense to a certified physician.
3. The manufacturer is required to conduct a Canadian phase IV observational study of Mifegymiso safety.
4. The manufacturer is required to administer a 24-hour bilingual support line.
5. The prescriber needs to obtain a consent for each patient wishing to take Mifegymiso.
6. The prescriber needs to provide a medication information and patient information card to each patient wishing to take Mifegymiso.

In addition to these post-authorization activities and restrictions, the Mifegymiso product monograph lists the following conditions that the physician must meet before prescribing Mifegymiso:[4,38]

1. Ensure that patients have access to emergency medical care for 14 days after taking Mifegymiso.
2. Schedule a follow-up visit seven to 14 days after administering Mifegymiso. This is mainly intended to confirm successful pregnancy termination.
3. Exclude ectopic pregnancy and confirm gestational age through ultrasonography.
4. Provide comprehensive counsel to the patient regarding the benefits and risks of Mifegymiso.
5. Obtain written informed consent from the patient.
6. Complete the training program and be registered to prescribe Mifegymiso.

APPENDIX 6: SUMMARY OF THE AUSTRALIAN PHASE IV STUDY

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize and critically appraise the post-authorization surveillance phase IV study conducted in Australia in accordance with the approval conditions.

Findings

Following the approval of mifepristone by the Therapeutic Goods Administration (TGA) of Australia, and at the TGA's request, the manufacturer monitored the efficacy and safety outcomes of patients treated with 200 mg mifepristone followed by buccal misoprostol 800 mcg for early medical termination of pregnancy. The manufacturer established a noninterventional post-authorization safety study titled "Phase IV Study: Assessment of the safety of mifepristone 200 mg followed by buccal misoprostol 800 mcg in early medical abortion in MSIA [Marie Stopes International, Australia] clinics," with the study number HREC2012001. The stated objective of Australian phase IV study was to "to describe the use of mifepristone in combination with buccal misoprostol in women undergoing an early medical abortion (EMA) in Australia following the approval of mifepristone and misoprostol by the Australian Therapeutic Goods Administration."[20]

In a literature search, we did not find any publications relevant to the phase IV study. As a result, the data and information presented in this appendix were collected from varying sources: the Health Canada's Reviewers' Report,[20] the Mifegymiso product monograph,[4] and the pharmacoeconomic-related reports in the submission to CADTH Common Drug Review (CDR).[19]

The phase IV study was a retrospective, observational, descriptive study initiated March 1, 2013, at Marie Stopes International, Australia (MSIA) clinics. The exact date the study ended is not clear. At the beginning of the study, the population and exposure in the study was assumed to match the initial Australian approval indication (gestational age of less than 49 days). However, pregnant women seeking elective medical abortion with a gestational age of more than 49 days but less than 63 days were also included in the study. Subsequently, the TGA extended the indication to cover up to 63 days' gestational age.[19,20]

The study reported on efficacy and safety outcomes; failure was defined as the need for surgical intervention; while safety outcomes included blood transfusion, vaginal bleeding, uterine spasm, breast tenderness, infections, pain, malaise, fatigue, pyrexia, lethargy, dizziness, syncope, diarrhea, vomiting, nausea, and hematemesis. Also, the study reported on the composite outcomes of "at least one adverse event," and "at least one serious adverse event," although we were unable to find a definition of what constituted an adverse event and a serious adverse event.

As an observational, descriptive study, the phase IV study had no comparison group. Categorical variables were presented with a total and percentage of the overall population, while continuous variables were presented with mean and standard deviation. No statistical comparisons were conducted among different gestational age groups of the phase IV study. It appears that the study's investigators conducted a quarterly interim descriptive analysis.

Beyond the gestational age and the age of women undergoing elective medical abortion, we could not find detailed characteristics of the population in the phase IV trial. From March 1, 2013, to September 30, 2013, 3,327 women were enrolled. The mean age of women in the study was 28.2 years (standard deviation 6.3 years, minimum 17 years, maximum 46 years); the mean gestational age was 45.9 days (standard deviation 6.42 days). It appears that the study aimed to follow-up with patients after a period of time (we were unable to find the exact period in referenced sources). The rate of women who were lost to follow-up in the period from March 1, 2013, to September 30, 2013, was an average of 14.2%.[20] We were unable to find the rate of women lost to follow-up in the rest of study period or in the overall study period.

The most recent findings from the phase IV study were provided in the pharmacoeconomic section of the manufacturer's submission;[20] the analysis covered a period from March 1, 2013, to December 31, 2015, with a total of 16,549 observations. The success rate for women seeking medical abortion with a pregnancy of gestational age up to 49 days was 96.3% (11,688/12,142), while the success rate for women with a pregnancy of gestational age between 49 and 63 days was 94.1% (4,145/4,407). Table 22 provides a summary of the cumulative method failure from each of the available time periods.

TABLE 22: RATE OF FAILURE OF ABORTION IN THE PHASE IV AUSTRALIAN STUDY

	Gestational Age ≤ 49 Days	Gestational Age 50 to 63 Days	Total
Data collected from study initiation (March 1, 2013) up to September 30, 2013			
Number exposed, N	2,809	518	3,327
Failure, n (%)	93 (3.3)	39 (7.5)	132 (4.0)
Data collected from study initiation (March 1, 2013) up to December 31, 2014			
Number exposed, N	8,165	2,717	10,882
Failure, n (%)	287 (3.5)	160 (5.9)	447 (4.1)
Data collected from study initiation (March 1, 2013) up to December 31, 2015			
Number exposed, N	12,142	4,407	16,549
Failure, n (%)	454 (3.7)	262 (5.9)	716 (4.3)

Sources: Health Canada's Reviewer's Report,[20] product monograph,[4] CDR submission.[19]

With regard to safety, the most recent data available in the pharmacoeconomic submission reported the total rate of women who experienced at least one adverse event at 16.6% (2,750/16,549); the rate of women who experienced at least one serious adverse event at 4.4% (728/16,549); and the rate of women who experienced vaginal bleeding at 2.4% (399/16,549). One death was reported in a woman with a pregnancy of gestational age 49 days or less. The cause of death was determined to be fulminating streptococcal pyogenes septicemia that originated from a lobar pneumonia and lung necrosis.

Table 23 provides the data on all safety outcomes with a rate higher than 1% that we were able to collect from the available resources.

TABLE 23: HARMS WITH A RATE OF MORE THAN 1%

	Gestational Age ≤ 49 Days	Gestational Age 50 to 63 Days	Total
Data collected from study initiation (March 1, 2013) up to September 30, 2013			
Number exposed, N	2,809	518	3,327
At least one AE, n (%)	499 (17.8)	93 (18.0)	592 (17.8%)
At least one SAE, n (%)	98 (3.5)	39 (7.5)	137 (4.1)
Vaginal bleeding, n (%)	75 (2.7)	32 (6.2)	107 (3.2)
Data collected from study initiation (March 1, 2013) up to December 31, 2015			
Number exposed, N	12,142	4,407	16,549
At least one AE, n (%)	2,021 (16.6)	729 (16.5)	2,750 (16.6)
At least one SAE, n (%)	461 (3.8)	267 (6.1)	728 (4.4)
Vaginal bleeding, n (%)	249 (2.0)	150 (3.4)	399 (2.4)

AE = adverse event; SAE = serious adverse event.
Sources: Health Canada's Reviewer's Report,[20] CDR submission.[19]

Critical Appraisal

The phase IV Australian study was a surveillance study employing an observational, descriptive design. Uncontrolled studies are unable to establish inferences, and any attempt at establishing inferences may lead to a false cause; also, they are unable to account, or control, for any possible confounder or effect-modifier that may affect the results. As an example, if high bleeding rates were observed, we cannot infer that these rates were caused by the intervention without a comparative group to assess differences in the baseline characteristics and to provide expected overall bleeding rates in the enrolled population.

In addition, the lack of available information on the exact method for selecting the study population means that we are unable to provide an opinion regarding the extent of selection bias in the study. For example, women who were residing in rural, underserviced, areas could be disproportionately selected for medical abortion. This is further confounded by the lack of detailed baseline patient characteristics. We do not know whether the study population had different characteristics from the general population, nor are we able to discuss whether certain risk factors had any effect on the rates of failure or of any adverse event. Also, the lack of information regarding the method of collecting data and the overall settings in which the study was conducted mean that we are unable to assess the accuracy and validity of the data used. For example, data are limited on how outcomes were adjudicated, whether this was performed uniformly and consistently among all participants, and whether these data were collected systematically.

From the limited information available, it appears there was a 14% rate of women lost to follow-up in the first six months of the study, but there is no available information on how the study investigators handled missing data, nor if this rate of follow-up affected the reported success rate. This further casts doubt on the validity of the result, given the lack of baseline characteristics and our inability to assess whether the women lost to follow-up had distinct characteristics that make them at higher or lower risk of failure or an adverse event. The rate of loss to follow-up usually biases the results in favour of the exposure, as study participants who are more proactive concerning their health gain positive outcomes, and those with fewer adverse events tend to follow-up with their physician.

On the other hand, the value of a surveillance study lies in providing data for planning, implementation, and evaluation of a public health practice. In the case of this phase IV study, the aim was to demonstrate the use and feasibility of the intervention, as well as the lack of any overt, public health–level signals of serious failure and/or harms. Health Canada has considered this phase IV study as providing valuable information regarding the real-world efficacy and safety of Mifegymiso. Indeed, it could be argued that, even in the absence of comparators, the results of the phase IV study show consistency with the results presented in the pivotal trials and are supported by our previous biological knowledge.

Conclusion

The phase IV Australian study of the mifepristone and misoprostol combination was a surveillance study employing an observational, descriptive design. The results of the study showed an overall success rate of 95.7% and an overall rate of serious adverse events of 4.4%. Since the study is descriptive, lacking a comparison, and provided little information on how it was conducted, it is best to view these results on their own without generalizing them and expecting the same rates in any other population, or contrasting the results with those from other interventions or populations.

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