Common Drug Review
Pharmacoeconomic 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.
Reimbursement 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
CMA	cost-minimization analysis
RCT	randomized controlled trial
SOGC	Society of Obstetricians and Gynaecologists of Canada

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Mifepristone and misoprostol (Mifegymiso)
Treatment	Mifepristone 200 mg orally as a single dose followed by 800 mcg misoprostol (4 tablets of 200 mcg) by the buccal route as a single dose 24 to 48 hours later
Comparators	Methotrexate plus misoprostol (100 mg plus 800 mcg) Vacuum aspiration in hospital Vacuum aspiration in a free-standing clinic
Study Question	The objective of this study was to perform a cost-minimization analysis of mifepristone plus misoprostol in women of childbearing age with a pregnancy of ≤ 49 days since the first day of the last menstrual period (LMP) who are choosing to end their pregnancy, compared with surgical abortion by vacuum aspiration or medical abortion by methotrexate plus misoprostol.
Type of Economic Evaluation	Cost-minimization analysis (CMA)
Target Population	Women of childbearing age with a pregnancy of ≤ 49 days since the first day of the last menstrual period (LMP) seeking early termination
Perspective	Canadian health care payer
Outcome Considered	Costs
Key Data Sources	
Clinical Efficacy	Naive estimates from disparate trials
Harms	Naive estimates from disparate trials
Cost	Physician billing: Ontario Schedule of Benefits and Fees 2003 Drugs: Ontario Drug Benefit Formulary 2003 Hospital (non-physician) services: Ontario Case Costing Initiative (OCCI) 2001–2003 Clinic costs for surgical abortion: Toronto clinic All costs, except the price of mifepristone plus misoprostol, were adjusted to 2016 values using a Canadian inflation calculator.
Time Horizon	From time seeking a termination (i.e., first visit to a physician) to end of follow-up visit (i.e., one to two weeks after an abortion)
Results in Manufacturer's Reference Case	The expected costs, from a health care payer perspective, were estimated to be: • Mifepristone plus misoprostol: $582.56 • Methotrexate plus misoprostol: $380.69 • Vacuum aspiration in hospital: $1,028.53 • Vacuum aspiration in clinic: $503.14
Key Limitations	• Misoprostol alone was omitted from the manufacturer's analysis. The CDR clinical review identified one comparative randomized controlled trial between mifepristone plus misoprostol and misoprostol alone and reported statistically significant higher rates of successful abortion for mifepristone plus misoprostol (relative risk at 49 days 0.82; 95% confidence interval, 0.74 to 0.90). This could not be examined within the context of cost-effectiveness given the manufacturer's economic analysis (CMA). The cost for a single course of treatment mifepristone plus misoprostol is up to $296 more than misoprostol alone.

	• Cost data used in the manufacturer's analyses were based on 2003 values, inflated to 2016, which may not accurately reflect current costs. Also, there was little exploration on the variability of surgical costs across Canadian jurisdictions. • Assumptions regarding resource utilization were not transparently described and justified. According to the CDR clinical expert, resource use was not reflective of existing Canadian practice. • Comparative efficacy and safety data were limited. The lack of data from RCTs or properly conducted indirect treatment comparisons to inform the treatment effect estimates in the manufacturer's model may impact the validity of the economic findings as selection bias and potential confounders may influence the results. • A CMA explicitly assumes no clinical difference between approaches to abortion, which may not hold as clinical studies suggest differences in success and complication rates among interventions. Specifically, surgical abortion appears to be associated with higher rates of success and lower complications rates compared with medical abortion approaches.
CDR Best Estimates	A reanalysis by CDR (accounting for current listed prices, validated probabilities and Canadian resource utilization) found that the expected cost, from a health care payer perspective, would be: • Mifepristone plus misoprostol: $610 • Methotrexate plus misoprostol: $410 • Misoprostol: $506 • Vacuum aspiration in hospital: $1,526 • Vacuum aspiration in clinic: $532

CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; LMP = last menstrual period; OCCI = Ontario Case Costing Initiative; RCT = randomized controlled trial.

EXECUTIVE SUMMARY

Background

Mifepristone and misoprostol (Mifegymiso) is a combination drug product comprising a progesterone receptor antagonist and a synthetic analogue of prostaglandin E1. It is approved by Health Canada for the medical termination of a developing intrauterine pregnancy with a gestational age up to 49 days.[1] Each box contains one 200 mg tablet of mifepristone and four 200 mcg tablets of misoprostol, and is administered as a sequential regimen of a single oral dose of mifepristone followed by a single buccal dose of misoprostol 24 to 48 hours later.[1] The individual ingredients of Mifegymiso cannot be sold separately, and the manufacturer's submitted confidential price for a single kit is $300.[2]

The manufacturer submitted a cost-minimization analysis (CMA) comparing mifepristone plus misoprostol to methotrexate plus misoprostol, vacuum aspiration in hospital, and vacuum aspiration in a free-standing clinic.[2] The modelled patient population was broader than the Health Canada–approved population, as it included pregnant women up to 63 days of gestation. The manufacturer's analysis was based on a decision tree that captured treatment success and complications (i.e., excessive bleeding, infection). By the end of the model, pregnancy was considered terminated in all patients regardless of the initial abortion strategy. Under a health care system perspective, the manufacturer reported that the expected costs for mifepristone plus misoprostol were $582.56, which is $201.87 more than methotrexate plus misoprostol and $79.42 more than vacuum aspiration in clinic, but $445.97 less than vacuum aspiration in hospital (**Error! Reference source not found.** for additional details).

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) noted several key limitations and sources of uncertainty with the manufacturer's economic evaluation:

- One relevant off-label medical comparator was not considered. According to both the clinical expert consulted as part of this review and the most recent clinical practice guidelines,[3] misoprostol alone is also prescribed in Canada. The cost of a single course of treatment can range from $3.51 to $5.27, depending on the dosage, which is considerably less than one course of mifepristone plus misoprostol. One comparative randomized controlled trial was identified from the clinical review that reported statistically significant higher rates of complete abortion at 49 days of gestational age for patients on the mifepristone plus misoprostol regimen compared with misoprostol alone (relative risk 0.82; 95% confidence interval, 0.74 to 0.90). This, however, could not be explored within the manufacturer's economic analysis, as a CMA was submitted.
- By submitting a CMA, the manufacturer assumes no differences in clinical effect that cannot be captured in the costs. Limited clinical data from noncomparative studies suggest higher rates of abortion failure and complications with mifepristone plus misoprostol compared with surgical approaches, which may result in greater disutility for patients on mifepristone plus misoprostol when compared with surgical abortion.
- Most of the probabilities in the manufacturer's model could not be validated.
- The CDR clinical review did not identify any relevant head-to-head randomized controlled trials comparing mifepristone plus misoprostol with the comparators included in the manufacturer's economic analysis. The relative efficacy and safety associated with each treatment strategy represent naive estimates — treatment-specific probabilities were taken from different studies, essentially breaking randomization. As a result, the validity of this data remains unknown, and potential selection bias and confounding may influence the results.

- The CDR clinical expert noted that resources utilization captured under each treatment strategy of the model does not reflect current clinical practice. There are instances in which this biases both in favour and against mifepristone plus misoprostol.
- Costs in the economic analysis were based on adjusting 2003 values to 2016 prices using the Bank of Canada inflation rate.[4] This approach can be less accurate, especially when more recent published costing data are available.
- The patient population modelled is not aligned to the current Health Canada indication. Mifepristone plus misoprostol is indicated in pregnant women with pregnancies of a gestational age up to 49 days, whereas the treatment estimates in the model were based on studies recruiting pregnant patients with pregnancies of a gestational age up to 63 days.

CDR performed a reanalysis to address, where possible, the identified limitations (namely, the inaccurate approach to cost adjustment, probabilities that could not be validated, and nonreflective Canadian resource utilization). The results of the CDR reanalysis were similar to the manufacturer's base-case results; the total costs associated with mifepristone plus misoprostol for women with a pregnancy of ≤ 63 days who are choosing to end their pregnancy was $609.55. This was more expensive than a medical regimen of methotrexate plus misoprostol (cost difference: $200), misoprostol alone (cost difference: $77), or surgical abortion by vacuum aspiration in the clinic (cost difference: $89), but less expensive than vacuum aspiration in a hospital setting (cost difference: $916).

Conclusions

At the current market price of $300 per course of treatment, mifepristone plus misoprostol was found to be more expensive and would result in additional costs, if listed, compared with methotrexate plus misoprostol, misoprostol alone, and surgical abortion in a clinic setting. The following price reductions would be required to achieve cost neutrality, depending on the comparator: 66% compared with methotrexate plus misoprostol, 26% compared with misoprostol, and 30% compared with surgical abortion in a clinic setting. When abortion in a hospital setting is the appropriate comparator, mifepristone plus misoprostol represents a cost-saving option.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis (CMA) comparing mifepristone plus misoprostol with methotrexate plus misoprostol, vacuum aspiration in hospital, and vacuum aspiration in a free-standing clinic.[2] This model was adapted from a previous publication by Limacher et al.[5] The analysis was undertaken from the perspective of a Canadian health care payer with a time horizon encompassing the first visit to a physician to seek an abortion until one to two weeks after a successful abortion. No justification was provided for why a CMA was appropriate.

The modelled population was broader than the licensed Health Canada indication, as women with a pregnancy of up to 63 days' gestation seeking an abortion were considered. The CMA was developed using a decision tree and considered abortion failure and two treatment-related adverse events (excessive bleeding and infections). Treatment-specific probabilities for success and complications were naive estimates derived from a variety of literature sources. In the case of medical abortion, a second dose of misoprostol can be administered if abortion is incomplete after the first dose. A follow-up physician visit, one to two weeks after the initial medical treatment, would be scheduled to confirm the completeness of abortion by ultrasonography. In the case of surgical abortion, completeness of abortion was assumed to be evident, and no further laboratory testing would be required. Surgical abortion by vacuum aspiration was performed in patients with a failed abortion. The probability of a complete abortion was 97.0% for surgical approaches, while for medical approaches to abortion, the probability of successful abortion (i.e., not requiring surgical abortion) was 95.2% for mifepristone plus misoprostol and 91.0% for methotrexate plus misoprostol (calculated by CADTH Common Drug Review [CDR] reviewers based on combining the manufacturer's transition probabilities).

The direct costs considered included treatment costs (including a dispensing fee of $11.24), the costs of additional treatment for incomplete abortion, and the costs of managing treatment-related complications. Sources of costing data were primarily from the Province of Ontario and included the Schedule of Benefits and Fees for physician and diagnostic/laboratory services, the Ontario Drug Benefit Formulary for medication costs (with the exception of mifepristone plus misoprostol), the Ontario Case Costing Initiatives for hospital expenses, and a Toronto abortion clinic for procedure costs in a clinic setting. Costs were based on 2003 Canadian values and adjusted to 2016 prices using the Bank of Canada inflation rate.[4] Indirect costs relating to time loss from work in either the patient's workplace or home (i.e., assuming an average hourly earnings of $21.06) was considered under the societal and patient perspectives. Specifically, the patient perspective considered the cost of medication and the time loss from work while the societal perspective considered all direct and indirect costs. All results were calculated deterministically.

2. MANUFACTURER'S BASE CASE

The manufacturer calculated that health care costs were greater for mifepristone plus misoprostol ($582.56) compared with methotrexate plus misoprostol ($380.69) or vacuum aspiration in clinic ($503.14) but were lower than vacuum aspiration in hospital ($1,028.53) (Table 2). Details on the findings under the patient and societal perspectives can be found in Table 12 of APPENDIX 4: REVIEWER WORKSHEETS.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S REFERENCE CASE

	Cost Categories ($)				Total Health Care Payer Cost ($)	Cost Difference (Compared With Mifepristone plus Misoprostol) ($)
	Treatment Cost[a]	Management of Complications	Physician Costs	Diagnostic Costs		
Mifepristone plus misoprostol	311.36	0.27	171.30	99.64	582.56	[reference]
Methotrexate plus misoprostol	59.56	0.51	210.19	110.42	380.69	–$201.57
Vacuum aspiration in hospital	524.06	25.78	350.65	128.04	1,028.53	$445.97
Vacuum aspiration in clinic	292.46	13.16	92.11	105.41	503.14	–$79.42

[a] Includes pharmacists' dispensing fee, if applicable.
Source: Manufacturer's submission.[2]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer conducted a one-way deterministic sensitivity analysis on three of the model parameters (i.e., probability of complete abortion, price of mifepristone plus misoprostol, and cost of surgical abortion). The range tested for the probability of complete abortion was based on the reported range in literature, while the range for prices was selected arbitrarily. The manufacturer's submission noted that the only variable to which the model was sensitive was the cost of mifepristone plus misoprostol, as its price can vary from CAD$11.52 to CAD$148.11, based on international pricing reported by Limacher et al.[5] However, the manufacturer only presented detailed findings from a price range of CAD$290 to CAD$310; under this range, the model's findings remained consistent with the manufacturer's base case. Under a societal or patient perspective, mifepristone plus misoprostol was found to be cheaper than surgical abortion regardless of the setting in which vacuum aspiration is performed.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CDR identified the following key limitations and sources of uncertainty with the manufacturer's CMA.

4.1 Appropriate Comparator Omitted

The manufacturer's submission stated that mifepristone plus misoprostol is not intended to replace surgical abortion, but rather to provide women with an alternative when surgical abortion is contraindicated. Under this claim, the appropriate comparators for mifepristone plus misoprostol would be other medical abortion practices. Yet only one medical comparator was included in the manufacturer's economic analysis: methotrexate plus misoprostol. As noted in the most recent guideline by the Society of Obstetricians and Gynaecologists of Canada (SOGC)[3] and by the clinical expert consulted as part of this review, another medical regimen commonly used off-label in Canada for the early termination of pregnancy is misoprostol alone.

Drug cost for a single course of misoprostol alone is the lowest among medical abortion approaches (Table 5). Compared with mifepristone plus misoprostol, misoprostol alone is approximately $296 less per course of treatment, depending on the dosage. The clinical review identified one study comparing mifepristone plus misoprostol and misoprostol. The study was a randomized controlled trial (RCT) reporting statistically significantly higher rates of successful abortion as a result of mifepristone plus misoprostol (relative risk 0.82; 95% confidence interval, 0.74 to 0.90).[6] This cost–benefit trade-off cannot be effectively considered within the manufacturer's economic submission, as mifepristone plus misoprostol is a more expensive regimen in terms of drug costs but is also more effective than misoprostol alone.

4.2 Cost Adjustment and Jurisdictional Variation

The economic analysis was based on a publication by Limacher et al.,[5] which was based on 2003 prices. The costs from the manufacturer's model were based on adjustment of the 2003 values from Limacher et al.[5] inflated to 2016 prices using the Bank of Canada inflation rate.[4] Although adjusting costs by the inflation rate is a supported practice when up-to-date costing data are not available,[7] a more accurate approach would be to take prices from current fee schedules, where possible.[8-11]

In addition, the cost of surgical abortion is variable across Canadian jurisdictions and even depending on the setting where the surgery is performed. The potential variability in these costs was not adequately characterized in the manufacturer's submission. Furthermore, given a lack of reporting on how the cost of surgical abortion in the clinic was derived, the costs of surgical abortion in a clinic may not reflect true public-payer costs. When it is difficult to derive the cost paid by public payers, a proxy may be the cost listed by abortion clinics for uninsured patients, ranging from $400[12] to $500[13] compared with $292 assumed by the manufacturer.

4.3 Resource Allocation Not Reflective of Canadian Practice

The manner in which resources are captured under each treatment strategy does not reflect existing clinical practice, as confirmed by the clinical expert consulted by CDR. There are instances in which this biases the results both in favour of, and against, mifepristone plus misoprostol. Furthermore, although the manufacturer attempted to provide both a societal and patient perspective, the calculations for these perspectives were not provided. As a result, CDR could not verify whether resource utilization was calculated correctly under these perspectives.

4.4 Uncertainty in Comparative Efficacy and Safety

As the CDR clinical review notes, there are no head-to-head RCTs comparing mifepristone plus misoprostol with surgical abortion or with methotrexate plus misoprostol. In the manufacturer's economic analysis, the rates of incomplete abortion and complications with each treatment strategy represent naive comparisons from a range of study types (e.g., reviews, partly randomized controlled trial, case reports, case series), and it is not clear whether the studies from which these rates were taken recruited patients with similar characteristics. The lack of data from RCTs or properly conducted indirect comparisons to inform the treatment effect estimates in the manufacturer's model reduces the validity of the economic findings, as selection bias and potential confounders may have influenced the results.

Most probabilities in the manufacturer's model could not be validated. In comparing the probabilities in the manufacturer's model with existing systematic reviews,[14] Canadian abortion guidelines,[3] and large case series,[15-19] CDR noted that the probability of incomplete abortion (i.e., requiring a surgical intervention) may have been overestimated in the mifepristone plus misoprostol arm (manufacturer's

value, 4.8% versus CDR reanalysis, 3.2%).[3] The current Health Canada indication for mifepristone plus misoprostol is for a pregnancy with a gestational age up to 49 days, whereas the success rates in the economic model were based on studies recruiting patients with pregnancies of gestational age up to 63 days. Feedback from the CDR clinical expert noted that the success rates for medical abortion are inversely related to gestational age (i.e., lower success rates with increasing gestational age). As a result, the probability of successful abortion is likely underestimated, and this may have introduced an overestimation of the total costs associated with mifepristone plus misoprostol when compared with surgical abortion. The probability of incomplete abortion with surgical abortion strategies may also have been overestimated (manufacturer's value, 3.0% versus CDR reanalysis, 0.9%)[14,15] but underestimated in the methotrexate plus misoprostol strategy (manufacturer's value, 6.0% versus CDR reanalysis, 7.5%).[3]

4.5 Inappropriate Analysis

The justification for a CMA may be inappropriate, given the absence of direct or properly conducted indirect comparisons to support equivalent efficacy and safety of mifepristone plus misoprostol versus the comparators. The underpinning of a CMA is the assumption of no difference in clinically meaningful outcomes, including patients' preferences (i.e., utility) in terms of the method of abortion and treatment experience. This assumption may be inappropriate given different failure and complication rates between treatments. Given that the failure rate with mifepristone plus misoprostol is higher than surgical abortion, it may be reasonable to expect that medical approaches to abortion are associated with lower quality-adjusted life-years, given the need for a second procedure. How this relates to the benefits of patient choice and access (i.e., greater convenience) is also unclear. A CMA does not permit the analysis to capture patient preferences toward the approach to abortion (surgery versus medical), assumes no utility difference in approaches (e.g., between medical versus surgical abortion, or an abortion with no complications and an abortion with complications), and does not allow exploration of uncertainty.

5. CADTH COMMON DRUG REVIEW REANALYSES

CDR undertook several reanalyses to address the limitations previously described, when parameters could be reasonably revised in the submitted economic model. The CDR reference case incorporated the following revisions: revising costs according to current Canadian costing sources, adjusting patterns of resource utilization to reflect expected Canadian setting, and selecting validated probabilities.

Based on these changes, the result of the CDR reference-case analysis remained similar to the manufacturer's base-case results (Table 15 in APPENDIX 4: REVIEWER WORKSHEETS). Total costs with mifepristone plus misoprostol were $609.55; this was more expensive than a medical regimen of methotrexate plus misoprostol (cost difference: $200) or surgical abortion by vacuum aspiration in the clinic (cost difference: $89), but less expensive than vacuum aspiration in a hospital setting (cost difference: –$916).

The CDR reanalysis further incorporated a comparison to a misoprostol-alone regimen. Using the comparative success rates from the study identified in the clinical review (i.e., relative risk of complete abortion: 0.82),[6,20] the estimated total cost per patient was $532.17 under a misoprostol regimen, and the cost difference between mifepristone plus misoprostol to misoprostol was $77.

Based on the CDR base case, a price reduction of 66%, 26%, and 30% would be required for mifepristone plus misoprostol to be considered cost neutral with methotrexate plus misoprostol, misoprostol alone, and surgical abortion in a clinic setting (Table 3 and Table 4).

TABLE 3: CDR REANALYSIS PRICE REDUCTION SCENARIOS COMPARED WITH MEDICAL ABORTION TREATMENTS

Cost Difference of Mifepristone plus Misoprostol Versus Methotrexate plus Misoprostol			Cost Difference of Mifepristone plus Misoprostol Versus Misoprostol Alone
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**	**Reanalysis by CDR**
Submitted	201.87	200.00	77.38
10% reduction	171.88	170.00	47.38
15% reduction	156.89	155.00	32.38
20% reduction	141.89	140.00	17.38
25% reduction	126.90	125.00	2.38
30% reduction	111.90	110.00	–12.62
40% reduction	81.91	80.00	–42.62
50% reduction	51.92	50.00	–72.62
60% reduction	21.93	20.00	–102.62
70% reduction	–8.06	–10.00	–132.62

TABLE 4: CDR REANALYSIS PRICE REDUCTION SCENARIOS COMPARED WITH SURGICAL ABORTION IN A CLINIC

Cost Difference of Mifepristone plus Misoprostol Versus Surgical Abortion in a Clinic		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**
Submitted	79.42	89.29
10% reduction	49.43	59.29
15% reduction	34.43	44.29
20% reduction	19.44	29.29
25% reduction	4.44	14.29
30% reduction	–10.55	–0.71
40% reduction	–40.54	–30.71
50% reduction	–70.53	–60.71
60% reduction	–100.52	–90.71
70% reduction	–130.51	–120.71

6. ISSUES FOR CONSIDERATION

The following issues for consideration were noted by CDR in consultation with the clinical expert consulted for this review:

- As part of the Health Canada approval, mifepristone plus misoprostol has a restrictive distribution plan, with only trained and certified physicians permitted to prescribe this drug. This drug regimen is dispensed to physicians, and mifepristone must be taken in the presence of the prescribing physician or a medical staff. Given these restrictions by Health Canada, in some cases, the pharmacist will need to deliver the drug directly to physicians.
- The price of mifepristone plus misoprostol varies widely internationally. The manufacturer's submission noted that the 2003 price of mifepristone plus misoprostol ranged from C$118.42 in the US to C$9.21 in the India.[2] These prices are lower than the manufacturer's submitted confidential price of $300.

7. PATIENT INPUT

No patient group input was received for this submission.

8. CONCLUSIONS

Based on the CDR reanalyses, mifepristone plus misoprostol was more expensive than a medical regimen of methotrexate plus misoprostol or surgical abortion by vacuum aspiration in the clinic. Further, mifepristone plus misoprostol was also more expensive than a misoprostol-alone regimen. Price reductions of 66%, 30%, and 30% would be required for mifepristone plus misoprostol to cost the same as methotrexate plus misoprostol, misoprostol alone, and surgical abortion in a clinic setting, respectively. When abortion in a hospital setting the appropriate comparator, mifepristone plus misoprostol represents a cost-saving option.

APPENDIX 1: COST COMPARISON

There are both medical and surgical options for women seeking early termination of pregnancy, as confirmed by the CDR clinical expert. The clinical expert consulted as part of this review has deemed the comparator treatments presented in Table 5 and Table 6 to be appropriate and relevant to the Canadian setting. Medication costs are based on list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table. As a result, costs may not represent the actual costs to public drug plans.

TABLE 5: COST-COMPARISON TABLE FOR MIFEPRISTONE PLUS MISOPROSTOL AND OTHER MEDICAL ABORTION REGIMENS FOR THE TERMINATION OF INTRAUTERINE PREGNANCY WITH A GESTATIONAL AGE UP TO 49 DAYS

Intervention	Strength	Dosage Form	Unit cost	Recommended Dose	Cost for a Single Course of Treatment ($)
Mifepristone plus misoprostol (Mifegymiso)	**200 mg and 200 mcg**	**Tablets**	**$300.000[a] per kit**	**200 mg of mifepristone oral followed by 800 mcg misoprostol buccal 24 to 48 hours later**	**$300.00**
Methotrexate plus misoprostol (off-label)	50 mg/m^2 and 200 mcg	1 vial for injection, Tablets	8.9200 per 50 mg/2 mL vial, $0.4389 per tablet	50 mg/m^2 of methotrexate intramuscular, followed 3 to 5 days later by 800 mcg misoprostol, vaginal, buccal, or sublingual	$17.45[b]
Methotrexate plus misoprostol (off-label)	2.5 mg and 200 mcg	Tablets	$0.6325 per tablet, $0.4389 per tablet	50 mg of methotrexate orally, followed 3 to 5 days later by 800 mcg misoprostol, vaginal, buccal, or sublingual	$14.41
Misoprostol (off-label)	200 mcg	Tablets	$0.4389 per tablet	2 to 3 doses of 800 mcg misoprostol, vaginal, buccal, or sublingual every 3 to 24 hours, maximum daily dose 2,400 mcg	$3.51 to $5.27

[a] Manufacturer's submitted price.
[b] Dosage based on the average body surface area reported for Canadian women aged 20 to 39 of 1.76 m.[221]
Note: Drug prices reflect the Ontario Drug Benefit (ODB) Formulary (accessed January 2017),[8] unless otherwise indicated, and do not include dispensing fees.

TABLE 6: COSTS OF SURGICAL ABORTION PROCEDURES FOR THE TERMINATION OF INTRAUTERINE PREGNANCY WITH A GESTATIONAL AGE UP TO 49 DAYS

Intervention	Description	Cost (SD, If Applicable)	Source
Surgical abortion (i.e., vacuum aspiration) in a clinic setting			
Total Costs	Out-of-pocket fee referenced in clinics for patients without public insurance (includes surgical procedure, laboratory tests, and physician consult)	**$400 to $500**	Canadian abortion clinics[12,13,22]
Surgical abortion (i.e., vacuum aspiration) in a hospital setting			
Surgeon Fee	#S752 "Abortion induced by any surgical technique, up to and including 14 weeks' gestation"	$112	Ontario SoB[10]
Anesthesiologist Fee	6 units of anesthesia (does not capture premium); each unit of anesthesia is billed at $15.01	$90	Ontario SoB[10]
Hospital Cost	CACS grouper (applied for day surgery and ambulatory care): 2520 – D&C and other uterus intervention Principal procedure: 5PC91GA – D&C post-delivery/ abort 5PC91GC – aspirat & curet post-delivery/ abort	Day surgery: $985 ($476) Ambulatory care: $835 ($352)	OCCI, 2011[11]
Total Costs		**$1,037 to $1,187**	

abort = abortion; aspirat & curet = aspiration and curettage; CACS = Comprehensive Ambulatory Classification System; D&C = dilation and curettage; OCCI= Ontario Case Costing Initiative; SD = standard deviation; SOB = schedule of benefits.

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 7: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments *Reviewer to provide comments if checking "no"*	The model inputs lacked transparency. It was not possible to verify the sources from which model parameters values were derived. It was also not possible to determine how the calculation for societal and patient perspective was done. Only selected one-way sensitivity analyses were conducted, and the display of one-way sensitivity analysis did not align with the findings reported in the manufacturer's submission.		
Was the material included (content) sufficient?			X
Comments *Reviewer to provide comments if checking "poor"*	Additional information was requested from the manufacturer, which did not entirely address the uncertainties in the model, as sensitivity analyses were conducted on only three of the model inputs. No justification was provided as to how resources were allocated under each strategy.		
Was the submission well organized and was information easy to locate?			X
Comments *Reviewer to provide comments if checking "poor"*	See comments above.		

TABLE 8: AUTHORS INFORMATION

Authors of the pharmacoeconomic evaluation submitted to CDR			
☒ Adaptation of global model/Canadian model done by the manufacturer ☐ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 3: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENTS OF DRUG

The cost-effectiveness of mifepristone plus misoprostol for women who are choosing to end their pregnancy has been assessed by Pharmaceutical Benefits Advisory Committee (PBAC) in Australia[23,24] and the Scottish Medicines Consortium.[25] In particular, the first review by PBAC was for women seeking termination of intrauterine pregnancy of up to 49 days' gestation[23] and was subsequently reviewed to expand the indication to pregnancy of up to 63 days' gestation (Table 9).[24] Details on the Scottish Medicines Consortium submission is limited, given that it was based on an abbreviated submission submitted by the manufacturer in August 2013. In both agencies, mifepristone plus misoprostol has been recommended for used for the medical termination of pregnancy of up to 63 days' gestational age.

TABLE 9: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	PBAC (March 2013;[23] July 2014)[24]
Treatment	Mifepristone, tablet 200 mg, and misoprostol, tablet 200 mcg (GyMiso)
Indication	2013 submission: Termination of intrauterine pregnancy of up to 49 days' gestation 2014 submission: Termination of intrauterine pregnancy of up to 63 days' gestation
Comparator	Surgical abortion (STOP)
Price	Not reported
Similarities to CDR submission	• Cost analysis (factoring in costs to manage complications)
Differences from CDR submission	• Societal and patient perspective presented in the CDR submission
Issues noted by the review group	• Noninferior effectiveness between mifepristone plus misoprostol and STOP. • Clinical effectiveness of mifepristone plus misoprostol declines marginally when comparing gestational age 50 to 63 days with age 49 days or earlier. Compared with 49 days or earlier of gestation, later gestational ages are associated with higher rates of surgical evacuation (4.1% vs. 2.3%) and continuing pregnancy (0.6% vs. 0.3%). • Higher rates of complications in patients after 50 to 63 days' gestation when compared with before 49 days' gestation (method of failure requiring surgical intervention: 6.24% vs. 3.52%; vaginal bleeding: 5.3% vs. 2.83%; pain: 1.65% vs. 0.66%). Absolute numbers for adverse events are low. • Threshold analysis suggests treatment costs associated with mifepristone plus misoprostol would need to be increased considerably for mifepristone plus misoprostol to cease to be cost savings compared with surgical termination of pregnancy. • Utilization of mifepristone plus misoprostol has been lower than expected since listing (in 2013). Although the sponsor's claim that the primary barrier to utilization is related to medical indemnity insurance for clinicians wanting to provide medical termination of pregnancy, this was deemed beyond the remit of PBAC. Utilization of mifepristone plus misoprostol is not expected to increase to the point where it would pose a financial risk by expanding the indication to permit patients with a later gestational age. • Mifepristone plus misoprostol is not suitable for prescribing by nurse practitioners.
Results of	Mifepristone plus misoprostol remained less costly (total cost $745.30) than STOP (total

	PBAC (March 2013;[23] July 2014)[24]
reanalyses by the review group (if any)	cost $1,333.75), even under all realistic sensitivity analyses. Cost analysis was most sensitive to changes in the price of mifepristone, choice of anesthesia, and proportion of women admitted to hospital or day-hospital facilities.
Recommendation	*March 2013:* "PBAC recommended the listing of mifepristone plus misoprostol for termination of an intrauterine pregnancy of up to 49 days gestation on the premise of noninferior effectiveness against STOP." *July 2014:* "PBAC recommended the listing of mifepristone plus misoprostol composite pack for termination of an intrauterine pregnancy of up to 63 days' gestation on the basis of noninferior effectiveness against STOP, in line with the revised TGA-approved indication."

CDR = CADTH Common Drug Review; PBAC = Pharmaceutical Benefits Advisory Committee; STOP = surgical termination of pregnancy; TGA = Therapeutic Goods Administration; vs. = versus.

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a CMA comparing mifepristone 200 mg and misoprostol 800 mcg (Mifegymiso) with another medical regimen of methotrexate 100 mg and misoprostol 800 mcg, and with surgical abortion (vacuum aspiration) in either a hospital or clinic setting. The model was based on a previous economic evaluation by Limacher et al.,[5] with costs inflated from 2003 values to 2016 prices. Sources for the 2003 prices include the Ontario Drug Benefit (ODB) for medication, the Ontario Schedule of Benefits and Fees for physician services, the Ontario Case Costing Initiative (OCCI), and costs derived from a large Toronto clinic for surgical and hospital fees. A single pharmacist's dispensing fee of $11.24 was applied for medications related to medical abortion strategies.

Complications with resource and cost implications that were considered in the manufacturer's model included excessive bleeding and infection. Complications were assumed to be mutually exclusive (i.e., patients could suffer from only one complication) and independent of treatment response (i.e., patients with or without successful abortion would have equal likelihood of developing complications). It was further assumed, without clear justification, that complications were managed differently according to the approach: for medical abortion, this would equate to an emergency room visit, diagnostic tests (e.g., liver function test, complete blood count, hemoglobin/hematocrit) and, if applicable, medication; for surgical abortion, a hospital visit was assumed without any associated physician billing. Treatment following an incomplete abortion was also handled differently depending on the approach to abortion: for medical abortion, patients would receive a second dose of misoprostol, and, if unsuccessful, a surgical intervention. According to the clinical expert consulted for this review, this is consistent with current Canadian clinical practice. For surgical abortion, the surgical procedure would be repeated.

TABLE 10: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy (i.e., probability of success)	Efficacy in this model was defined as the success rate (i.e., also referred to as a "complete abortion"). For medical abortion approaches, a second dose of misoprostol may be given if the first course of treatment is unsuccessful; if abortion was not complete after the second administration of misoprostol, patients were assumed to undergo surgical abortion. It is important to note that probabilities appear to be derived from studies that recruited pregnant women with a pregnancy of gestational age up to 63 days.	CDR was unable to validate which sources the manufacturer's probabilities were based upon, given a lack of reporting. In comparing the parameters used by the manufacturer with published sources, there are biases both in favour of, and against, mifepristone plus misoprostol. The bias against medical abortion approaches is due to the fact that the success rates were taken from patients with a pregnancy of gestational age up to 63 days. As noted by the CDR clinical expert and in the literature, the success rates for medical abortion are inversely related to gestational age. The Health Canada indication is limited to pregnancies with a gestational age up to 49 days. However, a bias in favour of medical abortion also exists. The probability of incomplete abortion for surgical abortion was overestimated (manufacturer's value, 3.0% vs. CDR reanalysis value, 0.9%).
Resource use	The manufacturer did not report how resource utilization was derived. The Limacher et al. article,[5] notes that the	According to the CDR clinical expert, the resource utilization patterns did not reflect current practice. For instance, it was assumed that patients with

Data Input	Description of Data Source	Comment
	clinical pathway was developed based on literature review and consultation with six physicians from a variety of fields. It is important to note that this validation may be outdated, as this study was published in 2006.	infection would be prescribed an antibiotic regimen of gatifloxacin 400 mg once daily, a drug that has since been withdrawn. The inaccuracy in resource utilization biases the results both in favour of, and against, mifepristone plus misoprostol.
Adverse events (Indicate which specific adverse events were considered in the model)	The adverse events captured in the model included excessive bleeding and infection. The manufacturer did not report clearly the source from which the adverse event rates were derived.	CDR was unable to validate from which sources the manufacturer's adverse event probabilities were derived. Despite this, the rates seem aligned with those reported in other sources. Given that the absolute numbers for adverse events are low for both treatment strategies, the model is unlikely to be sensitive to this parameter.
Costs		
Mifegymiso	Provided by the manufacturer	
Drugs	Ontario Drug Benefit Formulary (2003) adjusted by the Bank of Canada inflation calculator[8]	The source of the data is reasonable, although the method by which costs were adjusted to determine the 2016 price led to an overestimate when it was compared with the updated formulary price.
Surgical abortion procedure (hospital setting)	OCCI and Ontario Schedule of Benefits	The source of the data is reasonable. However, it is unclear how the surgical costs were derived. The costs seem to underestimate the most recent sources (e.g., cost of surgical abortion in a hospital setting: $524.06 [manufacturer's model] vs. $1,013.60 [CDR]).
Surgical abortion procedure (clinic setting)	Private Toronto clinic (costing methodology not reported) and Ontario Schedule of Benefits	It is difficult to verify the methods used to derive these costs, given the lack of reporting. In using the list price of surgical abortion quoted by clinics for uninsured patients, the manufacturer's cost estimate would appear to be an underestimate.[12,13]
Physician fees	Ontario Schedule of Benefits (2003) adjusted by the Bank of Canada inflation calculator	The source of the data is reasonable, although the method by which costs were adjusted to determine the 2016 price led to an underestimate when it was compared with the updated physician fee schedule.
Adverse events	For drug-related complications, the cost was taken from the Ontario Schedule of Benefits and the Ontario Drug Benefit Formulary. For surgical-related complications, costs were taken from OCCI.	According to the clinical expert, there are no differences in the management of adverse events arising from surgical or medical abortion. The manufacturer's model was biased against surgery, as the management of complications arising from surgical abortion was more costly than the complications arising from medical abortion.
Productivity	2003 Statistics Canada hourly earning, adjusted by the Bank of Canada inflation calculator	The source of the data is reasonable, although the method by which costs were adjusted is inappropriate.

CDR = CADTH Common Drug Review; OCCI = Ontario Case Costing Initiative; vs. = versus.
Source: Manufacturer's submission.[2]

TABLE 11: MANUFACTURER'S KEY ASSUMPTIONS (HEALTH CARE PAYER PERSPECTIVE)

Assumption	Comment
Medical and surgical approaches to abortion are equivalent in terms of clinical effectiveness and safety. Any differences can be quantified monetarily and do not have an impact on patient's utilities.	This assumption stems from the cost-minimization analysis. Given the higher rates of incomplete abortion with mifepristone plus misoprostol compared with surgical abortion, it may be reasonable to expect that medical approaches to abortion are associated with greater disutility. However, this may be offset by the benefits of patient choice and access (i.e., greater convenience). Given that limited data are available, it is therefore difficult to determine whether therapeutic equivalence is demonstrated to justify a cost-minimization analysis.
The patient population of the studies from which naive treatment-specific probabilities were taken are assumed to be similar.	This assumption is unlikely to be appropriate. Treatment-specific probabilities were taken from a variety of observational studies, since no evidence exists from randomized controlled trials. Observational designs are prone to biases such as selection bias and confounding. It is unclear whether the studies used to estimate these probabilities controlled for these biases.
Probabilities of success and complications at 49 days were similar to the probabilities at 63 days.	This assumption is unlikely to be appropriate for medical abortion approaches. According to the CDR clinical expert, the probability of success is reduced with older gestational age. Therefore, the rates of complete abortion applied to the analysis may be lower than what is expected in real practice.
Adverse events incorporated in the analysis include excessive bleeding and infection.	Appropriate based on feedback from the clinical expert consulted by CDR. Other treatment-related adverse events were noted to be minor and to have no large resource utilization/ cost implications.
Complications arising from medical and surgical abortion were managed differently.	According to the CDR clinical expert, this is not appropriate. The complications would be treated similarly, regardless of the approach to abortion.
No mortality is associated with abortion procedure.	Appropriate; the mortality rates associated with abortion are low, and mortality is rare.
Time horizon of the model: first physician visit to seek an abortion until one to two weeks after a complete abortion.	Appropriate, based on feedback from the clinical expert consulted by CDR.

CDR = CADTH Common Drug Review.

Manufacturer's Results

From a health care payer perspective, the estimated total cost of mifepristone plus misoprostol ($583 per patient) was $202 more than the total cost of methotrexate plus misoprostol ($381 per patient) and $79 more than that of vacuum aspiration in the clinic ($503 per patient), but $446 less than that of vacuum aspiration in the hospital ($1,029 per patient) (Table 12).

TABLE 12: MANUFACTURER'S TOTAL AND INCREMENTAL COSTS OF MIFEPRISTONE PLUS MISOPROSTOL VERSUS COMPARATORS

	Health Care Payer Cost, $ (Compared With Mifepristone plus Misoprostol)	Patient Perspective Costs, $ (Compared With Mifepristone plus Misoprostol)	Societal Perspective Costs, $ (Compared With Mifepristone plus Misoprostol)
Mifepristone plus misoprostol	582.56	1,089.90	1,691.56
Methotrexate plus misoprostol	380.69 (–201.57)	986.88 (–103.02)	1,469.37 (–222.19)
Vacuum aspiration in hospital	1,028.53 (445.97)	1,171.25 (184.37)	2,225.15 (755.78)
Vacuum aspiration in clinic	503.14 (–79.42)	1,171.25 (184.37)	1,820.09 (405.06)

Source: Manufacturer's submission.[2]

The manufacturer conducted deterministic sensitivity analyses on three model parameters: the probability of complete abortion with mifepristone and a single dose of misoprostol, the price of a single course of mifepristone plus misoprostol, and the cost of surgical abortion (Table 13). The selection for the range of parameter values tested in the sensitivity analysis was, for the most part, not clearly justified. In the manufacturer's report, it was noted that the only variable to which the model was sensitive was the cost of mifepristone plus misoprostol, as its price, in India and the US, varies from C$11.52 to C$148.11. However, in presenting the results of the sensitivity analysis, the manufacturer only varied the cost of a single course of treatment of mifepristone plus misoprostol between $290 and $310. The results of the analysis were robust across this price range tested.

TABLE 13: MANUFACTURER'S TOTAL AND INCREMENTAL COSTS OF MIFEPRISTONE PLUS MISOPROSTOL VERSUS COMPARATORS IN SENSITIVITY ANALYSIS

Sensitivity Analysis	Mifepristone plus Misoprostol, Total Cost	Methotrexate plus Misoprostol	Vacuum Aspiration in Hospital	Vacuum Aspiration in Clinic
		Total cost (Incremental Cost, Compared With Mifepristone plus Misoprostol)		
Reference Case	**$582.56**	**$380.69 (–201.87)**	**$1,028.53 (445.97)**	**$503.14 (–79.42)**
Probability of complete abortion with mifepristone and single dose of misoprostol *Reference: 0.925 / Sensitivity analysis: 1.00*	$567.15	$380.69 (–186.46)	$1,028.53 (461.38)	$503.14 (–64.01)
Probability of complete abortion with mifepristone and single dose of misoprostol *Reference: 0.925 / Sensitivity analysis: 0.90*	$587.7	$380.69 (–207.01)	$1,028.53 (440.83)	$503.14 (–84.56)
Price of single course of mifepristone plus misoprostol, *Reference: 300 / Sensitivity analysis: 310*	$592.56	$380.69 (–211.87)	$1,028.53 (435.97)	$503.14 (–89.42)

Sensitivity Analysis	Mifepristone plus Misoprostol, Total Cost	Methotrexate plus Misoprostol	Vacuum Aspiration in Hospital	Vacuum Aspiration in Clinic
		Total cost (Incremental Cost, Compared With Mifepristone plus Misoprostol)		
Reference Case	**$582.56**	**$380.69 (–201.87)**	**$1,028.53 (445.97)**	**$503.14 (–79.42)**
Price of single course of mifepristone plus misoprostol *Reference: $300 / Sensitivity analysis: $290*	$572.56	$380.69 (–191.88)	$1,028.53 (455.96)	$503.14 (–69.42)
Cost of medical fees associated with surgical abortion *Reference: $524.06 [hospital], $292.46 [clinic] Sensitivity analysis: $576.47 [hospital], $321.71 [clinic]*	$582.56	$380.69 (–201.87)	$1,080.90[a] (498.37)	$532.39 (–50.17)
Cost of medical fees associated with surgical abortion *Reference: $524.06 [hospital], $292.46 [clinic] Sensitivity analysis: $471.65 [hospital], $263.21 [clinic]*	$582.56	$380.69 (–201.87)	$976.12 (393.56)	$473.90[b] (–108.67)

[a] Total cost reported by manufacturer was $1,082.19 but may represent a typographic error.
[b] Total cost reported by manufacturer was $476.55 but may represent a typographic error.
Source: Manufacturer submission of addition material to CDR (December 13, 2015).[26]

CADTH Common Drug Review Reanalyses

CDR identified several limitations and parameters that were associated with uncertainty in the manufacturer's model. Accordingly, CDR undertook several one-way and multi-way reanalyses to test the robustness of the manufacturer's results. Table 14 summarizes the reanalysis undertaken by CDR.

TABLE 14: CDR MULTI-WAY DETERMINISTIC REANALYSIS RESULTS

Sensitivity Analysis	Mifepristone plus Misoprostol, Total Cost	Methotrexate plus Misoprostol	Vacuum Aspiration in Hospital	Vacuum Aspiration in Clinic
		Total cost (Incremental Cost Compared With Mifepristone plus Misoprostol)		
Manufacturer's Reference Case	**$582.56**	**$380.69 (–201.87)**	**$1,028.53 (445.97)**	**$503.14 (–79.42)**
1) Resource utilization reflects Canadian practice	$607.21	$448.37 (–184.00)	$1,044.79 (412.43)	$405.04 (–227.32)
2) (1) and costs updated	$625.60	$421.59 (–203.94)	$1,529.80 (913.37)	$520.02 (–92.32)
3) Probabilities based on values validated by CDR	$581.99	$377.97 (–204.02)	$1,030.49 (448.50)	$499.88 (–82.11)

Resource Allocation

CDR reviewers noted that the resource utilization assumed in the model was not reflective of current Canadian practice. Issues with the manufacturer's submission included:

- *Different groups of clinicians offering different medical abortion services*: In the manufacturer's model, mifepristone plus misoprostol was assumed to be administered in a family practice setting, whereas a specialist's clinic was assumed for methotrexate plus misoprostol. The clinical expert consulted in this review noted that no difference should be expected in terms of which health care providers prescribe each of these drug regimens.
- *Frequency of physician visits:* In some instances, the methotrexate plus misoprostol regimen was associated with one to three additional unexplained obstetrician consultations. According to the CDR clinical expert, there should be no difference in the number of physician visits between these two drug regimens.
- *Misallocation of laboratory services*: The performance of laboratory tests for each treatment strategy was incorrectly allocated. For instance, the manufacturer's model omitted the costs of liver function tests that would be required for the methotrexate plus misoprostol strategy and included renal tests for all patients receiving mifepristone plus misoprostol. Similarly, with respect to patients undergoing surgical abortion, feedback from the CDR clinical expert noted that, outside of blood typing, other laboratory testing is rarely required. However, the manufacturer's model incorporated, without proper justification, several laboratory tests in the surgical abortion strategies (i.e., alanine aminotransferase, aspartate aminotransferase, and creatinine). Furthermore, certain laboratory tests were billed together, ignoring the restrictions stated in the Schedule of Laboratory Fees[9] (e.g., complete blood count and hemoglobin-hematocrit were billed together).
- *Incorrect billing codes for specialists offering medical abortion*: The manufacturer's model assumed a general consultation and follow-up visit for the services of a specialist in the medical abortion group. The clinical expert consulted as part of this review provided feedback that, within the Ontario Schedule of Benefits, specific billing codes exist (i.e., A920 and A921)[10] for obstetricians who provide medical management of early pregnancy.
- *Differences in the management of treatment-related complications*: The model assumed that complications would be managed differently according to the approach taken to terminate an early pregnancy. This appears not to be valid, as the CDR clinical expert stated that the treatment of infections and excessive bleeding arising from abortion would be managed similarly, regardless of the approach to the abortion. Furthermore, patients with cases of infection were assumed to be treated by a drug regimen (gatifloxacin) that has been withdrawn by Health Canada. In a CDR reanalysis, a different antibiotic regimen was assumed (i.e., doxycycline 100 mg twice daily, with or without metronidazole 500 mg twice daily, for seven to 10 days).

Other minor issues were identified by the CDR reviewer (e.g., inclusion of physician fee for an injection in patients undergoing surgery, omitting hospital fees for surgical abortion in patients failing medical abortion).

With resource utilization corrected to reflect Canadian practice and with the removal of pharmacists' dispensing fees, the CDR reanalysis estimated that the total cost for mifepristone plus misoprostol was $632 per patient (assuming medical termination of pregnancy is offered by a family practitioner). In this reanalysis, mifepristone plus misoprostol was $184 more than methotrexate plus misoprostol ($448 per patient) and $227 more than surgical abortion in a clinic ($405 per patient), but $412 less than surgical abortion in a hospital ($1,045 per patient).

Updating Outdated Prices to Current Values

Although CDR reviewers acknowledged that adjusting costs by the inflation rate can provide a proxy for current prices, it is important to understand that this can be an inaccurate method and can affect the estimated cost difference between different treatment strategies. The accuracy of the prices used in the manufacturer's model relies on an assumption that changes in pricing over time adhere to the rate of inflation. This may not always hold true and, when more current pricing is available, such prices would be preferred. In a CDR reanalysis, the prices for physician services, in-hospital treatment, and drugs were updated to reflect current fee schedules and costing databases,[8-11] and Canadian resource utilization patterns were assumed. The total cost of mifepristone plus misoprostol was $626 per patient and remained more costly than methotrexate plus misoprostol (cost difference: $204) and surgical abortion in a clinic (cost difference: $92) but was less expensive than surgical abortion in a hospital (cost difference: $913)

Validity of Clinical Estimates

As the clinical review noted, there is a lack of evidence directly comparing the Health Canada–approved regimen of mifepristone plus misoprostol with surgical abortion or methotrexate plus misoprostol. In the manufacturer's model, probabilities for treatment success and complications were taken from the publication by Limacher et al.[5] CDR reviewers were unable to validate these values. As a result, model probabilities were revised, with the selection of clinical estimates based on the following order: Canadian abortion guideline,[3] existing systematic review,[14] and case series (with a preference on studies in developed countries and those with larger sample size).[15-19] CDR noted that the rate of all unsuccessful abortions (i.e., defined, under the medical approach, as the proportion of patients proceeding to vacuum aspiration and, under the surgical approach, as the proportion of patients requiring a repeat aspiration) was overestimated in the mifepristone plus misoprostol (manufacturer's value, 4.8% versus CDR reanalysis, 3.2%) and surgical abortion strategies (manufacturer's value, 3.0% versus CDR reanalysis, 0.9%) but underestimated in the methotrexate plus misoprostol strategy (manufacturer's value, 6.0% versus CDR reanalysis, 7.5%). A CDR reanalysis with validated probabilities found this to have a marginal impact, as the total cost for mifepristone plus misoprostol ($582 per patient) was $204 and $82 more than that of methotrexate plus misoprostol ($378 per patient) and vacuum aspiration in a clinic ($500 per patient), respectively, and $449 less than that of vacuum aspiration in a hospital ($1,030 per patient). It is important to note that, due to data limitations, both the manufacturer and CDR reviewers selected estimates from noncomparative studies for the probabilities in the economic model; therefore, both represent naive indirect comparisons. Hence, there is a potential risk of selection bias and confounding with these clinical estimates, which may have affected the estimated cost difference observed between treatment strategies. The validity of the treatment effect estimates remains uncertain and, therefore, the validity of the economic model's finding is uncertain, given that the magnitude and direction of bias in the clinical estimates remain unclear.

It is important to note that the Health Canada indication is for pregnancies with a gestational age up to 49 days, whereas the economic model is based on data from patient populations up to a gestational age of 63 days. According to the clinical expert consulted as part of this review, the success rate for medical abortion is inversely related to gestational age (i.e., success rate of medical abortion decreases with increasing gestational age). Indeed, in a recent guideline of the Society of Obstetricians and Gynaecologists of Canada,[3] the reported success rate for abortion for a mifepristone plus misoprostol regimen ranged from 95.9% to 97% in patients seeking termination of a pregnancy with a gestational age up to 49 days. The range widened somewhat (i.e., 94.2% to 99.8%) for patients seeking termination of a pregnancy with a gestational age of 63 days.[3] Given that the manufacturer's model may have

underestimated the success rates for medical abortion, the total costs associated with medical regimens may be overestimated, given the additional cost to manage incomplete abortion. The extent of underestimation is unknown, given that the success rates in pregnant women with a gestational age up to 49 days is not known for every medical regimen.

The CDR reference case (Table 15) was based on the manufacturer's model with the following revisions:

- Canadian resource utilization assumed, per discussion with the clinical expert
- costing revised based on current fee schedules and databases[8-11]
- validated probabilities for treatment success and complications.[3,14-19]

In addition, the CDR reanalysis included an additional comparator for medical abortion, a misoprostol-alone regimen that reflects existing Canadian clinical practice guidelines.[3,27] This was the only intervention identified in the clinical review for which direct comparative evidence exists, and the clinical expert consulted in this review offered feedback that this remains a relevant medical abortion option for patients in Canada. The drug-specific costs associated with a course of misoprostol are lower than those of other medical abortion approaches (Table 5) and, compared with mifepristone plus misoprostol, the difference in drug costs can range from $295 to $296 per course of treatment, depending on the dosage.

TABLE 15: CDR REFERENCE-CASE RESULTS

Sensitivity Analysis	Mifepristone plus Misoprostol, Total Cost	Methotrexate plus Misoprostol	Misoprostol[a]	Vacuum Aspiration in Hospital	Vacuum Aspiration in Clinic
		Total Cost (Incremental Cost, Compared With Mifepristone plus Misoprostol)			
Manufacturer's reference case	**$582.56**	**$380.69 (–201.87)**	**NA**	**$1,028.53 (445.97)**	**$503.14 (–79.42)**
CDR revised reference case	$609.55	$409.54 (–200.00)	$532.17 (–77.38)	$1,525.95 (916.40)	$520.26 (–89.29)

[a] The least conservative assumption (patients would require three doses of 800 mcg misoprostol) was assumed.

A series of one-way deterministic sensitivity analyses and scenario analyses were conducted on the CDR reference case for parameters associated with uncertainty and to reflect the potentially wide variation in clinical practice.

Specifically, the model was found not to be sensitive to the total cost of surgical abortion in a clinic setting, as mifepristone plus misoprostol remained more expensive than surgical abortion in a clinic when the list prices increased from $400 to $500 per procedure. Of interest, even when using the least conservative estimates for incomplete abortion requiring surgical intervention (i.e., 0%, 4%, 15%, and 0.5% for mifepristone plus misoprostol, methotrexate plus misoprostol, misoprostol alone, and surgical abortion by vacuum aspiration), the findings remained robust with mifepristone plus misoprostol (total cost: $570.31 per patient) being more costly than methotrexate plus misoprostol (cost difference: $209.52), misoprostol (cost difference: $77.38), and surgical abortion in a clinic setting (cost difference: $51.59), but less costly than surgical abortion in a hospital setting (cost difference: $954.10). This is indicative that similar economic findings may have been reached if the patient population had been restricted to women with a pregnancy of a gestational age up to 49 days.

Of note, prescribing mifepristone plus misoprostol is restricted to trained and certified physicians, given the post-authorization restrictions imposed by Health Canada. The CDR estimates were based on the assumption that medical abortion would be provided by a family physician. Scenario analysis assuming obstetricians would prescribe this medication was found to have marginal impact on the economic model.

TABLE 16: CDR SENSITIVITY AND SCENARIO ANALYSIS OF CDR REFERENCE-CASE MODEL

Sensitivity Analysis	Mifepristone plus Misoprostol, Total Cost, $	Methotrexate plus Misoprostol	Misoprostol	Vacuum Aspiration in Hospital	Vacuum Aspiration in Clinic
		Total Cost (Incremental Cost, Compared With Mifepristone plus Misoprostol), $			
CDR revised reference case	**609.55**	**409.54 (–200.00)**	**532.17 (–77.38)**	**1,525.95 (916.40)**	**520.26 (–89.29)**
Hospital cost for surgical abortion[a11] *Reference case: $1,013.6* *Sensitivity analysis [min cost]: $196.55*	585.03	348.26 (–236.77)	365.00 (–220.04)	708.90 (123.86)	520.26 (–64.78)
Total cost of surgical abortion in clinic *Reference case: $400*[12] *Sensitivity analysis: $500*[13]	609.55	409.54 (–200.00)	532.17 (–77.38)	1,525.95 (916.40)	620.26 (–10.71)
Probability of incomplete abortion requiring surgical intervention *Scenario analysis: upper bound estimates*[3,14]	648.78	458.29 (–190.49)	562.49 (–86.29)	1,527.48 (878.70)	521.79 (–126.99)
Probability of incomplete abortion requiring surgical intervention *Scenario analysis: lower bound estimates*[3,15]	570.31	360.79 (–209.52)	501.84 (–68.47)	1,524.41 (954.10)	518.72 (–51.59)
Type of practitioner providing medical abortion services *Reference case: family practitioners* *Scenario analysis: specialists*	688.17	487.59 (–200.58)	611.47 (–76.71)	1,525.95 (837.77)	520.26 (–167.92)
Alternative route of administration for methotrexate *Reference case: intramuscular (50 mg/m^2)* *Scenario analysis: oral (50 mg)*	609.55	402.60 (–206.94)	532.17 (–77.38)	1,525.95 (916.40)	520.26 (–89.29)

Sensitivity Analysis	Mifepristone plus Misoprostol, Total Cost, $	Methotrexate plus Misoprostol	Misoprostol	Vacuum Aspiration in Hospital	Vacuum Aspiration in Clinic
		Total Cost (Incremental Cost, Compared With Mifepristone plus Misoprostol), $			
CDR revised reference case	**609.55**	**409.54 (–200.00)**	**532.17 (–77.38)**	**1,525.95 (916.40)**	**520.26 (–89.29)**
Confirmation of success of medical abortion *Reference case: US ($49.65)* *Scenario analysis:* beta-hCG *($15.51)*	570.47	366.25 (–204.22)	498.03 (–72.44)	1,525.95 (955.48)	520.26 (–50.21)

beta-hCG = beta human chorionic gonadotropin; CDR = CADTH Common Drug Review; US = ultrasonography.
[a] Costs reported in OCCI database were from 2011. Value was adjusted by the Canadian consumer price index.[28]

Price-Reduction Analysis

To assess the impact of potential price variability across jurisdictions for surgical procedures and to determine the price at which mifepristone plus misoprostol would achieve cost neutrality, CDR conducted analyses to explore the relative savings or additional costs associated with mifepristone plus misoprostol when compared with methotrexate plus misoprostol, misoprostol alone, and surgical abortion in a clinic setting across various price-reduction scenarios. In the reference case, mifepristone plus misoprostol incurred additional costs compared with the comparators.

As shown in Table 17, a price reduction of 50% to 75% would be required for mifepristone plus misoprostol to be cost-saving when compared with methotrexate plus misoprostol. Specifically, a price reduction of 66% was required for mifepristone plus misoprostol to be cost-neutral to methotrexate plus misoprostol. Likewise, when compared with misoprostol, the cost of mifepristone plus misoprostol would need to be reduced by 26% to be cost-neutral.

TABLE 17: PRICE-REDUCTION SCENARIOS FOR MIFEPRISTONE PLUS MISOPROSTOL VERSUS METHOTREXATE PLUS MISOPROSTOL OR MISOPROSTOL ALONE

	Mifepristone plus Misoprostol Cost (Savings) of Single Course of Treatment				
	Submitted Price: $300	**10% Reduction: $270**	**25% Reduction: $225**	**50% Reduction: $150**	**75% Reduction: $75**
Methotrexate plus misoprostol $17.4548	200.00	170.00	125.00	50.00	(25.00)
Misoprostol alone $5.2668 [a]	77.38	47.38	2.38	(72.62)	(147.62)

[a] Assumes three doses taken in misoprostol-alone strategy.

The analysis was found to be most sensitive to the total cost of surgical abortion in a clinic (Table 18). If the price of surgical abortion was reduced by 50% or more, even up to a 75% price reduction for mifepristone plus misoprostol, surgical abortion would remain the lower-cost option. If the cost of surgical abortion in a clinic remained at $400,[12] a price reduction of 30% would be required for mifepristone plus misoprostol to be cost-neutral to surgical abortion in a clinic.

TABLE 18: PRICE-REDUCTION SCENARIOS FOR MIFEPRISTONE PLUS MISOPROSTOL VERSUS SURGICAL ABORTION IN A CLINIC

		Mifepristone plus Misoprostol Cost (Savings) of Single Course of Treatment				
		Submitted Price: $300	**10% Reduction: $270**	**25% Reduction: $225**	**50% Reduction: $150**	**75% Reduction: $75**
Surgical abortion in a clinic	**Reference price: $400**	89.29	59.29	14.29	(60.71)	(135.71)
	10% reduction: $360	129.29	99.29	54.29	(20.71)	(95.71)
	25% reduction: $300	189.29	159.29	114.29	39.29	(35.71)
	50% reduction: $200	289.29	259.29	214.29	139.29	64.29

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