#### Sun Pharmaceutical Industries Europe B.V.

## POST-AUTHORISATION SURVEILLANCE STUDY OF THE EFFICACY AND SAFETY OF MEDABON (MIFEPRISTONE/MISOPROSTOL) FOR EARLY PREGNANCY TERMINATION

Medabon (mifepristone/misoprostol)

### Protocol No. PASS-001 PROTOCOL VERSION: 1.0, 12 December 2011

Drug Development Phase:	IV
Sponsor:	Sun Pharmaceutical Industries Europe B.V. Polarisavenue 87 2132JH Hoofddorp The Netherlands Telephone: +31-(0)23-5685501 Telefax: +31-(0)23-5685505
Sponsor Representative	Juliette Omtzigt, General Manager RA/QA/PV Email: juliette.omtzigt@sunpharma-global.com
Incorporating Amendment no.	0.1
Issue Date	19 August 2013
Replaces Version (date)	N/A

#### **Confidentiality Statement**

This protocol is a confidential document owned by Sun Pharmaceutical Industries Europe B.V. Any unpublished information contained in it may not be disclosed to a third party without prior written approval of Sun Pharmaceutical Industries Europe B.V. However, the document may be disclosed to an independent Ethics Committee (EC) or a statutory regulatory authority under a similar condition of confidentiality.

## **PROTOCOL SYNOPSIS**

Name of Sponsor/Company: Sun Pharmaceutical Industries Europe B.V.

**Name of Finished Product:** Medabon<sup>®</sup> combination pack of 1 tablet of mifepristone 200 mg and 4 vaginal tablets of misoprostol 200 micrograms

Name of Active Ingredients: mifepristone and misoprostol

**Title of Study**: Post-authorization surveillance study comparing the efficacy and safety of Medabon (mifepristone/misoprostol) to historical data for early pregnancy termination

**Study Centres:** 3 centres across Europe: Karolinska Hospital, Stockholm, Sweden; the Helsinki University Central Hospital, Helsinki, Finland; and the University Department of Obstetrics and Gynaecology, Aberdeen, Scotland

#### **Phase of Development:** IV

#### **Objectives:**

To collect descriptive outcome data on the rate of incomplete abortion and continuing pregnancy, as well as the rate of adverse events related to the use of Medabon, in women requesting medical abortion with 63 days or less of gestation, as an additional pharmacovigilance measure in the risk management strategy for Medabon in Europe.

#### Methodology:

This is an open-label, non-interventional, prospective, observational, post-authorization study of the outcomes and safety associated with the use of Medabon for the medical termination of developing intra-uterine pregnancy of up to 63 days of amenorrhoea. This study is designed to obtain descriptive information on the safety and efficacy of Medabon in women undergoing termination of early pregnancy, and to evaluate and compare the emergency evacuation rate, continuing pregnancy rate and requirement for surgical intervention to the historical rates for this combination treatment. Subjects requesting medical abortion for which treatment with mifepristone/misoprostol is medically appropriate will be treated with Medabon per institutional practice and according to the European Summary of Product Characteristics, and followed for at least 14 days for treatment outcome, adverse events, and the requirement for other subsequent interventional treatment.

Number of Subjects: at least 500 (170 per study site)

#### **Diagnosis and Main Criteria for Inclusion:**

- Pregnant women with 63 days or less of gestation, requesting abortion and eligible for legal termination of pregnancy
- Subjects for whom mifepristone/misoprostol is a medically appropriate treatment for the termination of pregnancy
- Willing and able to sign informed consent
- Willing and able to complete a 10 to14-day follow-up visit
- Not participating in an interventional trial

#### Test Product, Dose and Mode of Administration, Batch Number:

Routine administration of Medabon (mifepristone/misoprostol) prescribed from commercially available pharmacy stock per institutional practice and according to the European Summary of Product Characteristics.

#### Duration of observational period and study:

From the first visit to the hospital/clinic through the follow-up visit at 10 to 14 days after the first visit (administration of mifepristone). If standard institutional ethical practice allows, data from routine contact with the subject at 30 days will also be collected in the electronic Case Report Form (eCRF).

The anticipated study duration is dependent on the enrolment rate by the study sites. The study will last approximately 6 to 8 months and will start shortly after commercialisation of the product in the respective countries and after Ethics Committee approvals and/or consensus or all three sites have been obtained.

#### **Criteria for Evaluation:**

Efficacy:

- The rate of incomplete abortion and continuing pregnancy at the time of the follow-up visit (10 to 14 days after the administration of mifepristone)
- The requirement for subsequent surgical evacuation

Safety:

- The emergency evacuation rate (because of haemorrhage or other reason)
- Incidence of adverse events related to Medabon treatment
- Necessity for additional medical treatment related to the termination of early pregnancy, such as the use of antibiotics to treat genital infections

#### **Statistical Methods**:

This study is designed to obtain descriptive information on the safety and efficacy of Medabon in women undergoing termination of early pregnancy. Data tabulations will be presented. Descriptive statistics will be used to characterise the subject population undergoing termination of early pregnancy.

The combination of mifepristone and misoprostol has been in clinical use for medical abortion for over a decade and event rates have been well established for emergency evacuation (1% to 2%), continuing pregnancy (less than 1%) and requirement for subsequent surgical evacuation (less than 6%). Event rates in this study will be compared to the expected event rates for this treatment regimen based on the historical data from a previous study by WHO using appropriate statistical methods and giving regard to differences between study sites, that may be dependent on country specific regulations.

## TABLE OF CONTENTS

PR	ото	COL SYNOPSIS	2
TA	BLE	OF CONTENTS	4
LI	ST O	F ABBREVIATIONS	7
1.	INT	RODUCTION	8
	1.1	Background	8
	1.2	Clinical Studies	9
		1.2.1 Clinical Studies With the Combination Regimen of 200 mg Mifepristone Orally	
		Followed by 800 µg Misoprostol Vaginally (WHO 97903)	9
		1.2.2 Clinical Studies with Medabon	.12
	1.3	Known and Potential Risks and Benefits	.15
	1.4	Study Rationale	.15
•	1.5	Study Population	.16
2.	STU	DY OBJECTIVES	.16
3.	SIU 2 1	JDY DESIGN	10
	3.1	I ype and Design of Study	17
	3.2	2.2.1 Efficacy Endnainta	.17
		3.2.1 Efficacy Endpoints	.17
	22	S.2.2 Safety Engpoints	.1/ 10
4	SUB		.10 18
т.	4 1	Number of Subjects	.18
	42	Inclusion Criteria	.18
	43	Exclusion Criteria	.19
	44	Withdrawal Criteria	.19
5.	STU	JDY TREATMENT	.19
	5.1	Medabon	.19
	5.2	Treatment of Subjects	.20
	5.3	Concomitant Medications	.20
6.	SEQ	QUENCE OF PROCEDURES	.20
	6.1	General Conduct of the Study	.22
	6.2	Study Assessments During the Observational Period	.22
		6.2.1 Baseline Data to be collected	.22
		6.2.2 Day 1	.23
		6.2.3 Day 2-3	.23
		6.2.4 Follow-up Visit (Day 10 through Day 21)	.23
		6.2.5 Follow-up through Day 30 (Subject to Institutional and Ethical Practice)	.24
7.	PRC	DTOCOL PROCEDURES	.25
	7.1	Assessment of Efficacy	.25
	7.2	Assessment of Safety	.25
		7.2.1 Adverse Events	.26
		7.2.2 Serious Adverse Events	.26
		7.2.3 Procedure for Adverse Event Recording	.27
		7.2.4 Procedure for Serious Adverse Event Reporting	.27
0		7.2.5 Regulatory Reporting of Safety Events	.2/ 20
о. 0	rku Sta	JIOCOL DEVIATIONS	.20 28
9.	91	Sample Size	.20 28
	9.1	Definitions	29
	2. ر	9.2.1 Subject Population	.29
		9.2.2 Observational Period	.29

Juli	I marin	naceatical industries Europe D. V.	Tilla 0.1, 17 Tugust 2015
	9.3	Statistical Analyses	
		9.3.1 Demographic and Background Characteristics	29
		9.3.2 Statistical Analysis Methods	29
	9.4	Primary Outcome Variables	29
	9.5	Secondary Outcome Variables	
	9.6	Analysis of Safety Variables	
	9.7	Procedure for Amendments to Statistical Plan	
	9.8	Data Collection	
10.	STU	DY DRUG MANAGEMENT	
11.	REC	ORDS RETENTION	
12.	QUA	LITY CONTROL AND QUALITY ASSURANCE	
	12.1	Monitoring	
	12.2	Auditing	
13.	ETH	ICS AND RESPONSIBILITY	
	13.1	Informed Consent	
	13.2	Ethics Committee	32
14.	CON	FIDENTIALITY	
15.	PUB	LICATION POLICY	
16.	INVI	ESTIGATOR AGREEMENT	
17.	REF	ERENCES	
AP	PENE	DIX 1 - CAUSALITY ASSESSMENTS FOR ADVERSE EV	<b>ENTS37</b>
AP	PENE	DIX 2 – EUROPEAN SUMMARY OF PRODUCT CHARA	CTERISTICS
AP	PEND	DIX 3 – DAILY DIARY CARD TEMPLATE	

## LIST OF TABLES

1:	Treatment outcome by treatment group and gestational age after 200 mg mifepristone followed 36 to 48 hours later by various regimens of	
	misoprostol from the pivotal WHO study [WHO 97903] (applied regimen	
	shadowed)	10
2:	Efficacy of 600 mg versus 200 mg mifepristone in combination with 1 mg	
	of amenorrhea, respectively	11
3:	Subjects reporting side-effects and symptoms before mifepristone	
	administration, misoprostol administration, and at follow-up interviews	13
4:	Schedule of procedures and assessments	21

## LIST OF ABBREVIATIONS

AE	Adverse event
AER	Adverse Event Report
CI	Confidence interval
DCF	Data clarification form
eCRF	Electronic case report form
EC	Ethics Committee
EMA	European Medicines Agency
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ITT	Intent-to-treat
PMS	Post Marketing Surveillance
RCOG	Royal College of Obstetricians and Gynaecologists
RR	Relative risk
SAE	Serious adverse event
SAER	Serious Adverse Event Form
SPC	Summary of Product Characteristics

## 1. INTRODUCTION

This protocol describes an open-label, non-interventional, prospective, observational, postauthorization study of the outcomes and safety associated with the use of Medabon<sup>®</sup> (mifepristone/misoprostol) for the medical termination of developing intrauterine pregnancy of up to 63 days of amenorrhea. Data collected in this study will further characterize the emergency evacuation rate, continuing pregnancy rate and requirement for surgical intervention for subjects receiving Medabon compared to the historical rates for this combination treatment using the regimen of mifepristone (Mifegyne<sup>®</sup>, Exelgyn Laboratories) and misoprostol (Cytotec<sup>®</sup>, Pfizer) [WHO study 97903, Honkanen et al. 2004, von Hertzen et al 20031. Subjects requesting medical abortion for whom treatment with mifepristone/misoprostol is indicated will be treated with Medabon per institutional practice and according to the European Summary of Product Characteristics (SPC), and followed for at least 10 to 14 days for treatment outcome, adverse events (AEs), and the requirement for other subsequent interventional treatment. If standard institutional ethical practice allows, data from routine contact with the subject at 30 days will also be collected in the electronic Case Report Form (eCRF).

In accordance with Directive 2001/20EC and the principles of a non-interventional study, the data collected will reflect routine procedures and measurements normally recorded in the subject medical records. No additional diagnostic and monitoring activities will be applied to subjects, other than routine hospital procedures.

This study will be conducted in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements.

## 1.1 Background

Medabon is provided in a combination pack, consisting of 1 tablet of mifepristone 200 mg and 4 tablets of misoprostol 200  $\mu$ g. The mifepristone 200 mg dose is for oral administration, and misoprostol 800  $\mu$ g should be administered vaginally 36 to 48 hours later.

The combination regimen of mifepristone and a prostaglandin analogue as a non-surgical alternative to surgical termination of early intrauterine pregnancy is well established and has been in clinical use since mifepristone was first approved in France in 1988, in UK in 1991 and in Sweden in 1992. In 1999, mifepristone (Mifegyne) was approved via a mutual recognition procedure in several EU member states with France acting as reference member state. The registered dose of mifepristone in Europe is 600 mg followed 36 to 48 hours later by 0.4 mg oral misoprostol when the duration of pregnancy is < 49 days since the onset of last menstrual period. When the pregnancy is more advanced (i.e., 50 to 63 days since last menstrual period), the registered prostaglandin analogue is gemeprost 1 mg vaginally.

In several trials, however, the effective dose of mifepristone has been demonstrated to be 200 mg when followed by 800  $\mu$ g of vaginal misoprostol ( $\leq 63$  days of gestation) [WHO 1993; WHO 2000; WHO 2001]. In addition, there is an approved alternative posology with 200 mg of mifepristone for pregnancies up to 63 days of amenorrhea, provided the

Subsequent prostaglandin is vaginal gemeprost as reflected in the EU SPC of Mifegyne: "Alternatively, 200 mg of mifepristone can also be used in a single oral dose, followed 36 to 48 hours later by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam". In addition, this is the regimen recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom (RCOG, 2011). The mifepristone tablet in Medabon has been demonstrated to be bioequivalent to Mifegyne after oral administration in a bioequivalence study (WHO-A65037).

Misopristol is a synthetic prostaglandin E1 analogue, initially developed for oral administration and available in a 200- $\mu$ g dose for the treatment and prophylaxis of gastric ulcers (Cytotec). Misopristol 200  $\mu$ g is approved for medical abortion only in a few countries, whereas the off-label use of misoprostol for medical abortion (and for other obstetrical and gynaecological indications) is reported to be wide-spread within Europe, the USA and worldwide, most often by the vaginal route of administration.

The misoprostol vaginal tablets in the Medabon combination pack have been formulated for optimal vaginal absorption. As a result of this formulation, the rate and extent of absorption of misoprostol following vaginal administration of 800 µg misoprostol was found to be increased by approximately 70% with the Medabon vaginal tablets compared to Cytotec (WHO-A65037). The study showed no clear differences in the safety profiles of the two misoprostol products, although the absence of a statistical difference in the number of undesirable effects should be made with caution, given the size of the study. Since the European marketing authorization of Medabon was based on data from the pivotal WHO efficacy and safety study which was performed with Cytotec [WHO 97903] [Honkanen et al, 2004; von Hertzen et al, 2003], there are no conclusive data showing that the increased exposure to misoprostol with the Medabon formulation causes no additional undesirable effects compared to the same dose of Cytotec following vaginal administration. Therefore this post-authorization study will be conducted to allow a direct and robust assessment of the regimen of mifepristone and misoprostol.

#### 1.2 Clinical Studies

# 1.2.1 Clinical Studies With the Combination Regimen of 200 mg Mifepristone Orally Followed by 800 µg Misoprostol Vaginally (WHO 97903)

The European application for a Marketing Authorization for Medabon is based on data from the pivotal placebo-controlled double-blind study [WHO 97903] [Honkanen et al, 2004; von Hertzen et al, 2003] sponsored by the WHO, which showed that the combined effect of 200 mg mifepristone orally followed 36 to 48 hours later by 800 µg misoprostol (Cytotec) vaginally provides medical abortion in pregnancies up to 63 days of amenorrhea with an efficacy that appears comparable to that of the already approved regimen 200 mg mifepristone orally followed by 1 mg gemeprost vaginally, based on historical outcome rates. WHO 97903 was a multicentre, double-blind, randomized controlled trial to compare three treatment regimens of misoprostol: oral route with repeated doses of misoprostol; vaginal route without repeated doses of

Misoprostol (i.e., single 800  $\mu$ g vaginal dose), when used after pre-treatment with mifepristone for the termination of pregnancy up to 63 days of amenorrhea (Table 1). The vaginal/single dose treatment group is the same treatment regimen as Medabon.

Table 1:	Treatment	outcome k	by treatment	group and	gestational	age after	200 mg
mifepristo	one followed	36 to 48 h	ours later by	various reg	imens of mi	soprostol f	from the
pivotal W	HO study [\	WHO 9790	3] (applied re	egimen shad	owed)		

Misoprostol treatment	Days of	Complete abortion		Continuing pregnancy	
regimen	amenorrhea				
		Ν	%	Ν	%
O/O	≤49	221	93.6	0	0.0
Oral miso 800 µg + Oral	50-56	224	93.3	3	1.3
miso 400 $\mu g x 2 x V II^{a}$	≥57≤63	234	88.6	6	2.3
V/O	≤49	228	94.6	0	0.0
Vaginal miso 800 µg + Oral	50-56	229	93.1	1	0.4
miso 400 µg x2xVII <sup>b</sup>	≥57≤63	244	96.1	0	0.0
V-only	≤49	214	95.5	2	0.9
Vaginal miso 800 µg <sup>c</sup>	50-56	227	93.0	0	0.0
	≥57≤63	249	92.2	0	0.0
	≤49	663	94.6	2	0.3
All	50-56	680	93.2	4	0.5
	≥57≤63	727	92.3	6	0.8
	total	2070	93.3	12	0.5

a. O/O treatment group = 1 tablet of mifepristone (200 mg) for oral use on day 1, 4 tablets of misoprostol (200 μg each) in one dose for oral use on day 3,4 tablets of placebo to be used vaginally on day 3, 28 tablets of misoprostol (200 μg each) to be used twice daily for 7 days, on days 4 – 10.

b. V/O treatment group = 1 tablet of mifepristone (200 mg) for oral use on day 1, 4 tablets of misoprostol (200 μg each) in one dose to be used vaginally on day 3,4 tablets of placebo for oral use on day 3,28 tablets of misoprostol (200 μg each) to be used twice daily for 7 days, on days 4 – 10.

c. V-only treatment group = 1 tablet of mifepristone (200 mg) for oral use on day 1, 4 tablets of misoprostol (200  $\mu$ g each) in one dose to be used vaginally on day 3, 4 tablets of placebo for oral use on day 3, 28 tablets of placebo to be used twice daily for 7 days, on days 4 – 10.

Source: Table 15 of the WHO Study 97903 study report.

The pivotal WHO study suggests that with an initial oral dose of 800 µg misoprostol, despite additional repeat oral doses, the efficacy remained lower than when misoprostol was initially given vaginally, although the difference in complete abortion rate between oral and vaginal misoprostol up to 56 days of amenorrhea was not statistically significant. In more advanced pregnancies, i.e. in women with length of amenorrhea  $\geq$ 57 days, the vaginal route of 800 µg misoprostol (V/O and V-only groups) after 200 mg of mifepristone was significantly more effective than the oral route (O/O group) in achieving complete abortion. Women with  $\geq$ 57 days of amenorrhea receiving misoprostol orally (O/O) had almost three times higher risk of failure (Relative risk [RR] 2.9; 95% confidence interval [CI] 1.4 to 5.8) than women receiving misoprostol vaginally with additional oral treatment (V/O). The RR of having a failure in women with  $\geq$ 57 days of amenorrhea receiving misoprostol orally (O/O) was 1.5 times higher (RR 1.5; 95%CI 0.9 to 2.5) than in women receiving 800 µg misoprostol vaginally (V-only). Thus, the most effective of the three regimens tested in the pivotal WHO study was the one that gave 800  $\mu$ g vaginal misoprostol followed by 800  $\mu$ g oral misoprostol daily for 7 days (V/O).

Although the difference between the O/O and the V-only groups in complete abortion rate was not statistically significant, the O/O administration was associated with a 4.5 times higher risk of continuing live pregnancies when compared with the V-only group (RR 4.5; 95% CI 1.0 to 20.7).

The risk of continuing pregnancy increased with gestational age; out of the total of 9 continuing pregnancies in the O/O group, 6 were among women with length of amenorrhea 57 days or more. Among women with length of amenorrhea  $\geq$ 57 days, continued administration of oral misoprostol (V/O group) further improved the efficacy compared with a single dose of 800 µg of vaginal misoprostol (V-only group). It should be emphasized that continuing pregnancy is a worse outcome after medical abortion than incomplete abortion as it may go unnoticed for a long time.

Although 600 mg of mifepristone has been the approved dose with demonstrated efficacy on both the outcome complete abortion and continuing pregnancy, there are many published studies on the 200-mg dose of mifepristone in various combinations with different doses, routes of administration, and brands of prostaglandins. Based on previous randomized comparative studies by WHO [WHO 1993; WHO 2001], the 200-dose of mifepristone seems established in combination with a potent prostaglandin with regard to the outcome complete abortion (Table 2).

Table 2:Efficacy of 600 mg versus 200 mg mifepristone in combination with 1 mggemeprost vaginally for termination of pregnancy <57 days and 57-63 days of</td>amenorrhea, respectively

Study	Posology	Ν	Days of amenorrhea	Complete abortion %	Continuing pregnancy %
WHO 1993	mifepristone 600 + gemeprost 1 mg mifepristone 200 + gemeprost 1 mg	389 388	<57	94.3 93.8	0.3 0.5
WHO 2001	mifepristone 600 + gemeprost 1 mg mifepristone 200 + gemeprost 1 mg	447 449	57-63	91.7 92.4	1.6 1.3

## Clinical Safety

The adverse effects reported can be divided into those related to the early pregnancy situation (nausea, vomiting, breast tenderness, fatigue, dizziness, headache, fainting), to those related to the drugs (diarrhea, fever defined as temperature >38°C, and rash) and those related to the

abortion process (lower abdominal pain, bleeding). The majority of AEs associated with medical abortion are related to the prostaglandin, in particular gastrointestinal AEs.

Whereas most AEs were similar in the three groups in the pivotal WHO study, there were some differences between the three dose regimens in favor of the V-only regimen. The occurrence of nausea and vomiting was higher in the oral group than in the vaginal groups. Vomiting is a well known misoprostol related side effect. Also, diarrhea was reported significantly more often for subjects in the O/O or V/O groups. At 1, 2 and 3 hours after administration of misoprostol, diarrhea was more frequent in the oral group than in the vaginal groups. At the 2-week follow-up visit, 26% of women who continued with oral misoprostol twice daily for 1 week (O/O and V/O groups) reported diarrhea, compared with only 9% of subjects in the V-only group which took placebo for 1 week.

There was no difference between treatment regimens with regard to estimated duration or amount of vaginal bleeding. Ten subjects required surgical intervention for continuing vaginal bleeding or emergency incomplete abortion. There were 40 subjects with bleeding more or much more than in normal menses requiring uterotonics to stop bleeding. Blood transfusion was needed in 0.1% of all cases.

Suspected gynaecological infection was reported in 0.6% (13/2219) of subjects. Most were presumptive infections based on clinical symptoms of fever, lower abdominal pain and vaginal bleeding. Endometritis was defined in 7 cases. There were no serious or fatal infections in the study and all of the infection cases were manageable by antibiotic therapy and resulted in complete recovery. The incidence of fever (temperature  $\geq 38^{\circ}$ C) after administration of misoprostol was higher in the oral group than in the vaginal groups at 1 hour, but the opposite was found at 3 hours. After administration of misoprostol, the frequency of fever in the vaginal groups after 3 hours was 6% versus 4.5% in the O/O group at 2 hours (*P*<0.001).

In conclusion, there was little difference in AEs, lower abdominal pain and bleeding pattern between groups, whereas there were more gastrointestinal AEs in the groups taking oral misoprostol for 7 days. Thus, the regimen that was associated with the lowest frequency of AEs was the mifepristone 200 mg followed 36 to 48 hours later by 800  $\mu$ g misoprostol vaginally. The regimen provided with Medabon (200 mg mifepristone followed 36 to 48 hours later by 800  $\mu$ g misoprostol vaginally) appears to be a safe medical method of abortion in otherwise healthy women with pregnancy duration of up to 63 days of amenorrhea.

## 1.2.2 Clinical Studies with Medabon

## **1.2.2.1** Pharmacokinetic Studies

Four pharmacokinetic studies were performed with Medabon, including Study WHO-A65037, a single-dose parallel-group study comparing Medabon to the regimen of Mifegyne and Cytotec. In study WHO-A65037, bioequivalence was demonstrated for mifepristone versus Mifegyne for oral administration of the mifepristone tablet component in Medabon. However, the bioavailability of misoprostol is higher in the Medabon formulation compared with Cytotec, which is not a formulation intended for vaginal administration. After vaginal

administration of the misoprostol vaginal tablets in Medabon and Cytotec (800  $\mu$ g), it was shown that the rate and extent of absorption of the misoprostol vaginal tablets was increased by approximately 70% compared to Cytotec. There was no clear difference in safety signal in spite of this increased absorption. While the exposure of misoprostol from Medabon is higher than that with Cytotec, it is still in a range that has been extensively studied in the past and proven to be effective and safe [von Hertzen et al 2007; von Hertzen et al 2010; Tang et al 2003]. In addition, the systemic exposure of misoprostol was shown to be considerably higher after sublingual compared to vaginal administration [WHO A65037-2].

## 1.2.2.2 Safety and Efficacy Studies with Medabon

Safety and efficacy of Medabon was evaluated in a multicenter, randomized, controlled trial by WHO in 1077 pregnant women with gestation of less than 9 weeks (63 days) who received Medabon for the termination of pregnancy [Warriner et al, 2011]. This trial was conducted in five rural district hospitals in Nepal to assess outcomes of medical abortion services provided by mid-level healthcare providers and doctors. In this study, 535 subjects were randomly assigned to a doctor and 542 to a mid-level provider for oral administration of 200 mg mifepristone followed by 800µg misoprostol vaginally 2 days later, and followed up 10 to 14 days later. The primary endpoint was complete abortion without manual vacuum aspiration within 30 days of treatment. Abortions were recorded as complete, incomplete, or failed (continuing pregnancy). Serious adverse events (SAEs), such as hemorrhage necessitating blood transfusion and conditions necessitating hospitalization, were recorded.

The overall intent-to-treat complete abortion rate was 96.7%, the incomplete abortion rate 2.8%, and continuing pregnancy rate 0.5%. Complete abortion rate was 97.3% in women assigned to mid-level providers and 96.1% in women assigned to doctors. The risk difference for complete abortion rates between mid-level providers and doctors was 1 24% (95% CI: -0.53 to 3 02), which falls within the pre-defined equivalence range (-5% to 5%). Therefore, equivalence between mid-level healthcare providers and doctors was established for the primary endpoint of complete abortion.

No serious complications were noted in this trial. Subjects reported typical side effects such as nausea, vomiting, diarrhea, abdominal pain, chills, and fever with no difference by type of provider. Details can be found in Table 3 [unpublished data, provided by the WHO].

Reported side-effects and symptoms	Before mifepristone administration		Before misoprostol administration		3 hours post misoprostol administration		At follow up*	
	MLPs	Doctors	MLPs	Doctors	MLPs	Doctors	MLPs	Doctors
Number of subjects	542	535	540	533	540	533	515	513
Nausea	309 (57.0%)	285 (53.3%)	358 (66.3%)	335 (62.9%)	58 (10.7%)	80 (15.0%)	50 (9.7%)	37 (7.2%)

Table 3:Subjects reporting side-effects and symptoms before mifepristoneadministration, misoprostol administration, and at follow-up interviews

Medabon (mifepristone/ misoprostol) Sun Pharmaceutical Industries Europe B.V.

Reported side-effects and symptoms	Before mifepristone administration		Before misoprostol administration		3 hours post misoprostol administration		At follow up*	
	MLPs	Doctors	MLPs	Doctors	MLPs	Doctors	MLPs	Doctors
Vomiting	90	83	136	115	14	15	13	16
	(16.6%)	(15.5%)	(25.2%)	(21.6%)	(2.6%)	(2.8%)	(2.5%)	(3.1%)
Diarrhea	24 (4.4%)	21 (3.9%)	30 (5.6%)	26 (4.9%)	0 (0)	2 (0.4%)	10 (1.9%)	11 (2.1%)
Degree of abdominal	0.5	0.5	1.0	1.0	2.9	2.8	1.5	1.6
pain (NRS: 00-10)	(0.8)	(0.9)	(1.2)	(1.1)	(1.7)	(1.6)	(1.6)	(1.7)
Rash			2 (0.4%)	0 (0)	1 (0.2%)	0 (0)	3 (0.6%)	0 (0)
Chills-Shivering	38	28	64	45	22	20	27	24
	(7.0%)	(5.2%)	(11.9%)	(8.4%)	(4.1%)	(3.8%)	(5.2%)	(4.7%)
Fever >38°C	17	15	25	27	14	12	28	26
	(3.1%)	(2.8%)	(4.6%)	(5.1%)	(2.6%)	(2.3%)	(5.4%)	(5.1%)
Abnormal vaginal	48	47	50	46	2	0	26	23
discharge	(8.9%)	(8.8%)	(9.3%)	(8.6%)	(0.4%)	(0)	(5.0%)	(4.5%)
Other signs and symptoms	148	148	130	125	15	9	46	47
	(27.3%)	(27.7%)	(24.1%)	(23.5%)	(2.8%)	(1.7%)	(8.9%)	(9.2%)
Total reporting any symptom	354	347	403	390	403	390	126	117
	(65.3%)	(64.9%)	(74.4%)	(72.9%)	(74.4%)	(72.9%)	(23.2%)	(21.9%)

MLPs = Mid-level providers

\* Women were asked about side-effects that they experienced during the two-week period since leaving the clinic until the follow-up visit. Therefore, the percentages do not correspond to the actual situation at the follow-up visit.

Three additional clinical trials of Medabon include introductory studies in Nepal and Thailand and a prospective uncontrolled study in Vietnam [unpublished data]. Those studies aimed to determine the appropriate service delivery processes and activities that are necessary for the introduction of medical abortion and its inclusion in comprehensive abortion care; therefore, no rigorous data analysis was performed. However, the data from those studies provide substantial additional exposure in broader populations and clinical settings.

In the introductory study of Medabon in Nepal, during the first phase of the study (from January to June 2009), the complete abortion rate was 96% (1593/1657 women) [unpublished data]. The remaining 4% who experienced incomplete abortion were managed by manual vacuum aspiration. The rate of women who experienced complications was 0.6% (n=10; 2 women had heavy bleeding requiring blood transfusion and 8 women had suspected minor infection which were treated with oral antibiotics as out subjects). The rate of complication in

this study compared well with rates reported by other studies on Cytotec [Ashok et al, 1998; Shannon et al, 2004; WHO study 97903; WHO study A35148].

In the second phase of the study (from June to December 2009), the complete abortion rate was 98% (2511/2557 women) [unpublished data]. The remaining women reported ongoing pregnancy (n=33; 1.3%), bleeding/cramping (n=10; 0.4%), and ectopic pregnancy (n=3; 0.1%). The rate of ongoing pregnancies was higher than that seen in other studies, possibly because no ultrasound was done to confirm gestational age so some pregnancies may have been beyond 9 weeks. There were 4 cases of infection reported (0.2%); among these, one woman had complete abortion, one had an ongoing pregnancy, and two reported bleeding and cramping.

Pilot introduction of medical abortion with Medabon took place in 2012 in four hospitals in Thailand. A total of 200 women with pregnancies up to 9 weeks were treated and 96% of them had a complete abortion. There were no complications, and 97% of the women were satisfied or highly satisfied with this service model.

In the Vietnam study, Medabon was used for termination of pregnancy up to 9 weeks at central and provincial level and up to 7 weeks at district level in Vietnam, according to the local regulation. All women received 200 mg mifepristone orally on Day 1. On Day 2 to 3, the women received misoprostol vaginally or sublingually. Women with gestation of up to 7 weeks received a 400-µg dose, while women with gestation of up to 9 weeks received an 800-µg dose. Among 360 women enrolled, the overall complete abortion rate was 96.7%. Failures occurred in 3.3% of women, which included 1.9% incomplete abortion, 0.3% missed abortion, and 0.6% continuing live pregnancy and 0.6% undetermined outcomes [unpublished data]. When stratified by gestational age, the complete abortion rate was 97.8% among 139 women with up to 7 weeks of gestation, and 96.6% among 112 women with 7-8 weeks of gestation and 95.2% among 100 women with 8 to 9 weeks of gestation.

There were no severe complications. Lower abdominal pain was reported by 41.7% of the women and other side effects like nausea, vomiting, diarrhea by less than 10% of the women.

## 1.3 Known and Potential Risks and Benefits

Potential risks and benefits of Medabon are included in the SPC (Appendix 2).

## 1.4 Study Rationale

The efficacy and safety of the combination 200 mg mifepristone orally and 800  $\mu$ g misoprostol vaginally (using Cytotec oral tablets) for medical abortion in women with a pregnancy duration of  $\leq$  63days has previously been demonstrated in the pivotal WHO trial [WHO 97903]. However, since the pivotal WHO efficacy and safety study was performed with Cytotec, there is no knowledge about the potential undesirable effect difference with respect to the effects of misoprostol in Medabon. The Medabon product has a different vaginal misoprostol formulation, resulting in a 70% higher systemic exposure as compared to Cytotec after single dose vaginal administration. While data from clinical trials with Medabon suggest that neither efficacy nor safety is negatively affected by the higher exposure, there have been no studies designed to demonstrate efficacy/safety of Medabon compared with the same treatent regimen using Mifegyne and Cytotec. Therefore, as a

Confidential

pharmacovigilance measure in the overall risk management strategy for Medabon in Europe, this post-authorisation surveillance study will obtain descriptive information on the safety and efficacy of Medabon in women undergoing termination of early pregnancy, and compare the emergency evacuation rate, continuing pregnancy rate and requirement for surgical intervention to the historical rates for this combination treatment using Mifegyne and Cytotec [WHO 97903].

## 1.5 Study Population

The study will enroll consecutively treated pregnant women with 63 days or less of gestation, requesting abortion and eligible for legal termination of pregnancy who will receive Medabon per institutional practice and according to the European SPC, who are not participating in another interventional trial, and who are able to provide written informed consent.

## 2. STUDY OBJECTIVES

The objective of this study is to collect descriptive outcome data on the rate of incomplete abortion and continuing pregnancy, as well as the rate of AEs related to the use of Medabon, in women requesting medical abortion with 63 days or less of gestation, as an additional pharmacovigilance measure in the risk management strategy for Medabon in Europe.

#### **3. STUDY DESIGN**

In accordance with the non-interventional and observational requirements of a registry (Directive 2001/20EC), no additional diagnostic and monitoring activities will be applied to the consecutively-treated subjects providing informed consent, other than routine procedures that reflect routine activities of the centre. The assignment of a subject to a particular therapeutic strategy will not be decided in advance but must fall within current institutional practice, and the prescription and administration of Medabon must be clearly separate from the decision to include the subject in the registry.

Definitions are provided below as objective guidance for determining outcome variables. However, in all cases, the data captured in the eCRF should reflect the judgment of the treating physician at the time.

#### **3.1** Type and Design of Study

This is an open-label, non-interventional, prospective, observational, post-authorization study of the outcomes and safety associated with the use of Medabon for the medical termination of developing intrauterine pregnancy of up to 63 days of amenorrhea. This study is designed to obtain descriptive information on the safety and efficacy of Medabon in women undergoing termination of early pregnancy, and to evaluate and compare the emergency evacuation rate, continuing pregnancy rate and requirement for surgical intervention to the historical rates for this combination treatment. At least 500 subjects will be enrolled at 3 centers across Europe (Sweden, Finland and Scotland), 170 subjects per study site. The study will enroll consecutive subjects requesting medical abortion for which treatment with mifepristone/misoprostol is medically appropriate. Prior to enrollment, subjects will be required to provide informed consent to allow the use of their data in accordance with

Confidential

relevant local Data Protection laws. Subjects will be treated with Medabon per institutional practice and according to the European SPC. Data will be collected from Day 1 (the first visit to the hospital/clinic) through the follow-up visit at 10 to 14 days after the first visit (administration of mifepristone) and will be captured in an electronic case report form (eCRF). If standard institutional ethical practice allows, data from routine contact with the subject at 30 days will also be collected in the eCRF.

The anticipated study duration is dependent on the enrolment rate by the study sites. The study will last approximately 6 to 8 months and will start shortly after commercialization of the product in the respective countries and after Ethics Committee (EC) approvals and/or consensus of all three sites have been obtained.

#### **3.2** Study Endpoints

#### 3.2.1 Efficacy Endpoints

- The rate of incomplete abortion and continuing pregnancy at the time of the follow-up visit (10 to 14 days after the administration of mifepristone)
- The requirement for subsequent surgical evacuation

#### 3.2.2 Safety Endpoints

- Incidence of serious adverse events related to Medabon treatment, such as hemorrhage requiring blood transfusion, conditions necessitating hospitalization, serious infections etc.
- The emergency evacuation rate (because of hemorrhage or other reason)
- Necessity for any additional medical treatment related to the termination of early pregnancy, such as the use of antibiotics to treat genital infections.

#### 3.3 Schematic Diagram of Study Design



## 4. SUBJECT POPULATION

#### 4.1 Number of Subjects

Approximately 500 subjects will be included at 3 centers in Sweden, Finland and Scotland.

#### 4.2 Inclusion Criteria

In accordance with Directive 2001/20EC, this post-authorization study is non-interventional.

Subjects will be recruited from among women requesting legal termination of pregnancy who fulfill the following criteria:

- 1. Good general health
- 2. Older than the age of legal consent

- 3. Requesting medical abortion and eligible for abortion
- 4. The duration of pregnancy is not more than 63 days LMP when verified by ultrasound
- 5. The pregnancy is intrauterine (intrauterine amniotic sac seen in ultrasound examination) (in very early pregnancies the sac may not be seen)
- 6. Single pregnancy (relative contraindication)
- 7. Willing and able to provide written informed consent to the use of their data in accordance with relevant local Data Protection laws, policies and regulations

## 4.3 Exclusion Criteria

Subjects will not be eligible for the study if any of the following exclusion criteria apply:

- 1. Participation in other interventional clinical research studies involving the evaluation of investigational drugs or devices at the time of enrolment
- 2. Subjects for whom treatment with Medabon is not indicated according to the European SPC for Medabon (Appendix 2)

## 4.4 Withdrawal Criteria

All subjects have the right to withdraw consent to the use of their data, at any point during the observational period without prejudice. The investigator can discontinue any subject at any time if medically necessary. If for any reason subject observations were discontinued, the reason will be recorded on the eCRF and the Sponsor should be notified promptly.

It is imperative to obtain complete follow-up data during the observational period for all subjects wherever possible. Subjects will not be replaced in this study.

## 5. STUDY TREATMENT

As a non-interventional, observational study, routine administration of Medabon will be prescribed from commercially available pharmacy stock and used in accordance with institutional practice, and the approved European SPC (Appendix 2).

#### 5.1 Medabon

Medabon Combipack contains one mifepristone tablet and four misoprostol vaginal tablets. Each tablet of mifepristone contains 200 mg mifepristone. Each vaginal tablet of misoprostol contains 200  $\mu$ g misoprostol. Further details about the medicinal product can be found in the European SPC (Appendix 2).

## 5.2 Treatment of Subjects

Subjects will be given the tablet of mifepristone (200 mg) orally on Day 1. The tablet must be swallowed in the presence of a member of the study team who will record the date and time when the tablet was administered.

Misoprostol is to be administered 24 to 48 hours (Day 2 or 3) after taking mifepristone. Four tablets of misoprostol (200  $\mu$ g each) are to be inserted vaginally. Misoprostol may be self-inserted vaginally by either the subject herself or by the doctor or nurse, during a hospital visit or at home.

The subject or health worker should use their finger to push the four tablets one at a time into the vagina as far as they are able. Health workers who administer misoprostol vaginally should follow the instructions on the package insert and wear clean gloves. If women administer misoprostol vaginally themselves either at home or in the clinic, they should be advised to wash their hands first.

## 5.3 Concomitant Medications

The non-interventional spirit of this study requires no limitation with respect to concomitant therapy considered necessary by the treating physician. However, all relevant therapeutic regimens should be documented to the requirements of the eCRF. All treatment received by the subject should be as per standard of care and institutional practice.

## 6. **SEQUENCE OF PROCEDURES**

This study consists of a single observational period from the first visit to the hospital/clinic (Day 1, administration of mifepristone) through the follow-up visit at 10 to 14 days after Day 1 (Day 11 to Day 15). If standard ethical and institutional practice allows, data from routine contact with the subject at 30 days will also be collected in the eCRF.

The follow-up visit may take place at a health center or in the hospital (trial site) that treated the women, however, the hospital (trial site) will obtain follow-up report electronically, or telephonically from the health center to facilitate data capture for follow-up visit. Per prescribing information of Medabon, it is recommended that follow-up occur 10 to 14 days after administration of mifepristone. However, this period may be relaxed up to 21 days per routine follow-up standards at sites.

During this observational period, but prior to collecting subject data, eligibility and informed consent will be sought. All available data requirements of the eCRF arising from routine procedures that reflect routine activities of the center should be collected thereafter. The maximum duration of a subject"s participation is approximately 30 days from administration of Medabon. A schedule of procedures and assessments is presented in Table 4.

Study Assessment	Day 1	Day 3	Follow-up visit (Day 11 – 14) <sup>d</sup>	Day 30 <sup>a</sup>
Informed consent	X			
Demographics	X			
Medical, obstetrical and gynaecological history	X			
Pelvic Ultrasound	X		X <sup>b</sup>	
Administration of mifepristone (oral)	X			
Administration of misoprostol (vaginal)	-	X		
Interview of subject and review of diary card	-	Xe	X	
Determination of treatment outcome	<		X	>
Additional medical treatment related to the termination of early pregnancy	<		X	>
Adverse Event Reporting	<		X	>
Serious Adverse Event Reporting	<		X	>
Concomitant medications	<		X	>

Table 4:	Schedule of	procedures and	d assessments
----------	-------------	----------------	---------------

a. Follow-up through 30 days subject to institutional and ethical practice.

b. Ultrasound at the follow-up visit if judged necessary from clinical findings.

c. Assessment of complete abortion, incomplete abortion, missed abortion, continued pregnancy, or undetermined, on the basis of the subject's history and the clinical findings or pelvic ultrasound examination.

- d. The follow-up visit may take place at a health center or in the hospital (trial site) that treated the women, however, the hospital (trial site) will obtain follow-up report electronically, or telephonically from the health center to facilitate data capture for follow-up visit. Per prescribing information of Medabon, it is recommended that follow-up occur 10 to 14 days after administration of mifepristone. However, this period may be relaxed up to 21 days per routine follow-up standards at sites.
- e. If misoprostol is inserted vaginally by either the subject herself or by a doctor or nurse at a location different from the trial site, an electronic or telephonic interview of the subject will be conducted to review diary card information.

## 6.1 General Conduct of the Study

Written informed consent will be obtained for this study by the principal investigator or subinvestigator from all subjects before the performance of any protocol-specific data collection. This study will collect data on routine procedures and measurements normally recorded in the subject notes only. No additional diagnostic and monitoring activities will be applied to subjects, other than routine hospital procedures. Where available the following data will be collected from subjects from the first visit to the hospital/clinic (Day 1, administration of mifepristone) through the follow-up visit at 10 to 14 days after Day 1 (Day 11 to Day 15). If standard institutional practice allows, data from routine contact with the subject at 30 days will also be collected in the eCRF.

#### 6.2 Study Assessments During the Observational Period

The following procedures will be performed at each of the following time points and the following data will be collected in the eCRF.

#### 6.2.1 Baseline Data to be collected

- Date of hospital/clinic visit
- Demographic and biometric information (age, body weight, height, blood pressure, pulse rate)
- Ethnic group (in accordance with local Data Protection laws, policies and regulations)
- Basic medical history
- Obstetric and gynecological history including:
  - Previous gynecological surgery
  - Cycle length
  - Duration of menses
  - Never pregnant
  - Nulliparity
  - o Multiparity
  - Previous miscarriage
  - Previous induced abortion
- Length of amenorrhea (days)
- Present pregnancy
  - Uterine size (weeks)
  - Presence of sac /fetal heart activity
  - Presence of nausea, vomiting, diarrhea, fatigue, or dizziness

• Use of drugs during pregnancy

#### 6.2.2 Day 1

- Obtain informed consent
- Obtain medical and gynecological history
- Ultrasound examination to verify length of pregnancy and check that pregnancy is intrauterine
- Mifepristone administration (record date and time)
- Record time of expulsion if it occurs
- Record additional medical treatment related to the termination of early pregnancy
- Record AEs and SAEs
- Record concomitant medication

## 6.2.3 Day 2-3

- Brief interview of subject and review of diary card
- Misoprostol administration (record date and time)
- Record time of expulsion if it occurs
- Record additional medical treatment related to the termination of early pregnancy
- Record AEs and SAEs
- Record concomitant medication

#### 6.2.4 Follow-up Visit (Day 10 through Day 21)

- Brief interview of subject and review of diary card
- Determination of treatment outcome by medical interview, pelvic examination, and ultrasound examination, if judged necessary from clinical findings
- Record requirement for surgical evacuation, if applicable, and reason for surgical evacuation
- Record additional medical treatment related to the termination of early pregnancy
- Record AEs and SAEs
- Record Concomitant medication

#### 6.2.5 Follow-up through Day 30 (Subject to Institutional and Ethical Practice)

This is optional as none of the three centers in the study follow up to 30 days. However, wherever possible, medical records may be electronically accessed to note whether any additional treatments were needed up to 30 days after mifepristone.

- Determination of treatment outcome (if not previously determined)
- Record requirement for surgical evacuation, if applicable, and reason for surgical evacuation
- Record additional medical treatment related to the termination of early pregnancy
- Record AEs and SAEs
- Record Concomitant medication

#### 7. **PROTOCOL PROCEDURES**

#### 7.1 Assessment of Efficacy

The outcome of the treatment will be classified on the basis of the subject's history and the clinical findings at pelvic ultrasound examination, as follows:

- *Complete abortion:* confirmed by passage of the products of conception and by clinical findings at pelvic examination, and no emergency or elective curettage during the period up to the first menstruation or till last follow-up
- *Incomplete abortion:* products of conception passed but clinical or ultrasound signs of incomplete abortion, thus requiring curettage for completion
- *Missed abortion:* no products of conception passed and ultrasound evidence of retained gestational sac but no cardiac activity
- *Continuing pregnancy:* no products of conception passed and cardiac activity present on ultrasound
- *Undetermined:* those who had surgical termination of pregnancy before the outcome was known (e.g. women who discontinued their participation before follow-up) or who were lost to follow up

Subjects will be asked or investigated whether the products of conception were expelled and the date and time of expulsion will be recorded on the eCRF.

#### 7.2 Assessment of Safety

In this study, safety will be assessed by the incidence of SAEs related to Medabon treatment, the emergency evacuation rate (because of hemorrhage or other reason), and the necessity for additional medical treatment related to the termination of early pregnancy, such as the use of antibiotics to treat genital infections.

At admission, subjects are to be given a diary card to record days of vaginal bleeding and the occurrence of AEs for the duration of the study (using a check-list), as well as all medications taken since admission (using an open-ended question). At each clinic visit, investigators are to collect the safety data from the participants by a medical interview and review of their diary cards. At each visit, subjects will be questioned systematically by the investigators about any AEs they might have had. AEs and the treatment provided during the study should be recorded in the subject"s medical record. Those events that are serious in nature must be reported to the sponsor in an expedited manner (as per regulatory requirement, they should be record within 24 hours of awareness of the SAE), as described in Section 6.4.

Where possible, subjects experiencing AEs should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject if necessary until the event resolves.

The European SPC will serve as the reference safety information for this study (Appendix 2).

## 7.2.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the study drug was given are not to be considered AEs. Heavy bleeding that requires vacuum aspiration or curettage is to be regarded as an AE.

Apart from the common AEs listed in the diary card or subject forms, any other untoward medical occurrence in subjects which does not necessarily have a causal relationship with the treatment may be reported in the "Remark" box at the end of the form or in a separated "Adverse Event Report (AER)" form if there was no provision or sufficient space within the subject forms to properly record information on such AEs.

The relationship to study drug will be assessed by the investigator (see Appendix 1).

## 7.2.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in persistent or significant disability/incapacity,
- Requires in-subject hospitalization or prolongs hospitalization,
- Is a congenital anomaly/birth defect, or
- Is another medically significant event that, based upon appropriate medical judgment, may jeopardized the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. allergic bronchospasm requiring intensive treatment in an emergency department or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a myocardial infarction that may be considered minor could also be an SAE if it prolonged hospitalization.

## 7.2.3 Procedure for Adverse Event Recording

All AEs (non-serious and serious) should be documented in the source documents. AEs/SAEs that occur during the observational period, or notified to the physician at any time while the subject is participating in the study, must be assessed and reported to the sponsor via the eCRF, regardless of causal relationship to the study drug.

## 7.2.4 Procedure for Serious Adverse Event Reporting

In addition to entering each SAE on the appropriate page of the eCRF, the investigator **must** complete a Serious Adverse Event Report (SAER) for each SAE, regardless of causality by study medication, occurring during the observational period or notified to the physician at any time while the subject is participating in the study. The SAER must be submitted to the Drug Safety Officer or designee within 24 hours (from time at which the SAE is recognized). The Drug Safety Officer or designee will contact the investigator should it be necessary to clarify any of the event information. Wherever possible, the investigator should provide any follow-up information for the event to the Drug Safety Officer or designee (see title page of the protocol for contact information) as soon as it becomes available and up to the point the event has been resolved. Further and only if required by local regulations or procedures, the investigator should report these events to the EC and/or national regulatory authority. In any such cases the sponsor should be informed.

All deaths occurring within the observational period, or that the physician may become aware of whilst participating in the registry, must be reported as SAEs on a SAER, through the process described above, regardless of the cause and relationship to study drug.

## 7.2.5 Regulatory Reporting of Safety Events

The physician is not required to report any safety event to the European authorities directly during the observational period. The physician will report AEs to the study sponsor who will process them and report to the relevant Regulatory Agency as required. This will not preclude direct reporting of AEs by the investigator if required, in which case, the physician should inform the study monitor so that an appropriate reporting process can be agreed.

All AE and SAE reports will be reported by the sponsor to the applicable health authorities based on the pharmacovigilance requirements and timelines for a post-marketed product in place at the time. Should any event be separately reported to the authorities (e.g., using the *Spontaneous* reporting system), it is required that the event be copied to the sponsor, and the authority reference number should be captured in the eCRF to enable linkage to the subject level data in the study.

## 8. **PROTOCOL DEVIATIONS**

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact Sun Pharmaceutical Industries Europe B.V. (the sponsor), or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject"s safety in the study. The investigator and the sponsor will document this decision and collect this information in the eCRF. If applicable, the EC will be informed of all protocol changes by the investigator in accordance with the EC established procedure. No deviations from the protocol of any type will be made without complying with all the EC established procedures.

## 9. STATISTICAL PLAN

This is an open-label, non-interventional, prospective, observational, post-authorization study of the outcomes and safety associated with the use of Medabon for the medical termination of developing intrauterine pregnancy of up to 63 days of amenorrhea. Approximately 500 subjects will be enrolled at 3 centers.

This study is designed to obtain descriptive information on the safety and efficacy of Medabon in women undergoing termination of early pregnancy. Data tabulations will be presented. Descriptive statistics will be used to characterize the subject population undergoing termination of early pregnancy.

The combination of mifepristone and misoprostol has been in clinical use for medical abortion for over a decade and event rates have been well established for emergency evacuation (1% to 2%), continuing pregnancy (less than 1%) and requirement for subsequent surgical evacuation (less than 6%). Event rates in this study will be compared to the expected event rates for this treatment regimen based on the historical data from a previous study by WHO [WHO 97903] using appropriate statistical methods and giving regard to differences between study sites, that may be dependent on country specific regulations.

As with all observational studies and registries, any conclusions concerning the link between treatment and clinical outcomes can not be established formally.

The final study report and Risk Management Plan for Medabon in Europe will be provided to the relevant competent authorities by the sponsor.

#### 9.1 Sample Size

This study is designed to obtain descriptive information on treatment outcome and safety in subjects administered Medabon. The sample size determination was not based on statistical consideration. However, it is considered that 500 subjects will be sufficient to compare the event rates to the rates reported in the pivotal WHO trial [WHO 97903] for the outcome

parameters of emergency evacuation (1% to 2%), continuing pregnancy (less than 1%) and requirement for subsequent surgical evacuation (less than 6%).

## 9.2 Definitions

## 9.2.1 Subject Population

For this study, the intent-to-treat (ITT) population will be defined and used in the analysis and/or presentation of the data.

The ITT population will be defined as all subjects providing informed consent for the use of their data and receiving Medabon. The safety analysis will also be classified according to the actual treatment received.

## 9.2.2 Observational Period

The observational period for the study is considered from the first visit to the hospital/clinic when mifepristone is administered (Day 1) through the follow-up visit at 10 to 14 days after the administration of mifepristone. If standard institutional ethical practice allows, data from routine contact with the subject at 30 days will also be collected in the eCRF. Any event occurring after the defined observational period, even if collected on the eCRF, will not be included in the planned analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

#### 9.3 Statistical Analyses

Descriptive statistics and/or subject data listings will be used to summarize the data. Continuous variables will be summarized by means, standard deviations, medians, interquartile ranges, and minimum and maximum values. Categorical variables will be summarized by frequencies and percentages.

#### 9.3.1 Demographic and Background Characteristics

Subject demographic and baseline characteristics will be summarized. Where meaningful, country-level and historical comparisons to equivalent treatment group in the WHO study [WHO 97903] will be assessed.

#### 9.3.2 Statistical Analysis Methods

On reaching 500 subjects, descriptive statistics and data listings will be used to summarize the data for the purposes of review by the sponsor. Adequacy of the risk management strategy for Medabon in Europe and the impact of risk management interventions will be assessed throughout the study. On completion of the study, the final study report and Risk Management Plan for Medabon in Europe will be provided to the EMA.

#### 9.4 Primary Outcome Variables

The primary variable is the rate of incomplete abortion and continuing pregnancy at the time of the follow-up visit (10 to 14 days after the administration of mifepristone), the requirement

for subsequent surgical evacuation, and the requirement for emergency evacuation due to haemorrhage or other reasons.

### 9.5 Secondary Outcome Variables

Secondary outcome variables include the incidence of AEs related to Medabon, and the necessity for additional medical treatment related to the termination of early pregnancy, such as the use of antibiotics to treat genital infections.

#### 9.6 Analysis of Safety Variables

Frequency of AEs, SAEs and outcome variables will be summarized by body system, preferred term, and relationship to Medabon.

## 9.7 Procedure for Amendments to Statistical Plan

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that due to the study observations, some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical study report.

## 9.8 Data Collection

The eCRF will be used to collect all subject data assessments that will be used for evaluation of specified analyses.

## **10. STUDY DRUG MANAGEMENT**

Medabon and all concomitant medication should be prescribed from commercially available pharmacy stock. The administration and storage of medication should be in accordance with the approved European SPC (Appendix 2) and institutional policy.

#### **11. RECORDS RETENTION**

ICH guidelines (E6) require that essential documents be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms (DCFs) received from the sponsor. Such documentation is subject to inspection by the sponsor or its agents, or other regulatory agencies.

## 12. QUALITY CONTROL AND QUALITY ASSURANCE

#### 12.1 Monitoring

The sponsor has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and applicable regulations. The investigator, as part of their responsibilities, is expected to cooperate with the sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the study), the sponsor's monitor will visit the centers during the study in accordance with the Monitoring Plan set forth for this study as well as maintain frequent telephone and written communication. The investigator will permit the sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

Given the nature of a registry, it is considered that data will be verified at source (subject notes) on a "for cause" basis, determined by remote data entry reviewed in the eCRF. It is anticipated that source data verification will be conducted in up to approximately 15% of sites. A detailed description of the procedures to be employed can be found in the monitoring plan.

#### 12.2 Auditing

The sponsor may conduct audits at the study centers. Audits will include, but not be limited to, presence of required documents, the informed consent process, and comparison of the eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the sponsor immediately if this occurs, and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

#### **13.** ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, with the sponsor's standard operating procedures, and/or guidelines, European Union regulations, and the International Conference on Harmonization (ICH) GCP.

The investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol and GCP requirements. Also, the Principle Investigator must complete and sign the Investigator's Agreement. In signing, the investigator agrees to:

- Sign and adhere to the Investigator Agreement
- Participate in Investigator meetings as scheduled by the sponsor

- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Obtain written informed consent from each study participant before any study specific data collection is performed
- Complete all eCRFs with all available data collected
- Capture data from all subjects consecutively treated with Medabon at their center as per standard institutional practice
- In accordance with the non-interventional and observational requirements of a registry (Directive 2001/20EC), ensure no additional diagnostic and monitoring activities will be applied to subjects, other than routine procedures that reflect routine activities of the center
- Comply with all European Union requirements for investigators, and with all other applicable regulations and codes of approvals from ECs and other Regulatory Authorities.

## **13.1** Informed Consent

In accordance with applicable EU rules on post-authorization studies in Volume 9A of the rules governing medicinal products in the European Union, all subjects (or their guardian or legal representative) will provide written informed consent to the use of their data before entry into the registry.

Written informed consent will be obtained from all subjects (or their guardian or legal representative) before any data is collected. The investigator has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same EC responsible for approval of this protocol. Each informed consent form shall include the elements required to the enable use of subject data in accordance with relevant local Data Protection laws, policies and regulations. The investigator agrees to obtain approval from the sponsor of any written informed consent form used in the study, preferably prior to submission to the EC.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the investigator (or designee) shall sign the EC-approved written informed consent form. The subject shall be given a copy of the signed informed consent form, and the original shall be kept in the site's regulatory file. A second copy may be filed in the subject's medical record, if allowed by the institution.

## **13.2** Ethics Committee

This is a non-interventional study that will be conducted in compliance with the protocol and in accordance with applicable EU rules on post-authorization studies as described in Volume 9A of the rules governing medicinal products in the European Union.

The aim of this study is to collect data from subjects who receive treatment with Medabon. The decision to use Medabon and thereby to enroll subjects resides with investigators. The study is an observational and non-experimental registry, and it is considered that the subjects enrolled are at no additional or particular medical risk from participation. All therapeutic decisions are made by the responsible investigators on the basis of individual subject cases without any requirements defined by the study protocol. The only prerequisite of the registry is the commitment of documentation. All data collected must reflect routine activities of the centers, and non-routine activities should not be carried out.

Each hospital site is responsible for determining whether or not ethical approval is necessary to implement the study at their particular site. Due to the type of data being recorded, and the fact that the study is observational (i.e., not testing a specific drug), the protocol will not require ethical approval at all sites. Other relevant authorities (Competent Authorities, Data Protection Agencies) will be notified or asked for approval of the protocol according to local requirements, and all EU sites must comply with the EU privacy directives in place at the time.

If required, this protocol and the written informed consent form shall be submitted to the EC identified with this responsibility at the research facility. Notification in writing of approval must come from the EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the EC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an EC member, the written approval must indicate such non-participation. The investigator will submit status reports to the EC as per local requirements. The EC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the EC all changes in research (protocol amendments) and will not make such changes without EC approval except where necessary to eliminate apparent immediate hazards to human subjects. The investigator will promptly report to the EC all unanticipated problems involving risk to subjects or others. The investigator is required to maintain an accurate and complete record of all written correspondence with the EC and must agree to share all such documents and reports with the sponsor.

## 14. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the sponsor. However, authorized regulatory officials and sponsor personnel (or designee) will be allowed full access to the records.

Only initials and unique subject numbers in the eCRF will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

## **15. PUBLICATION POLICY**

The investigators agree to keep strictly confidential all unpublished information and results concerning this study. Unpublished information must not be published or disclosed without the sponsor's prior written approval. The sponsor reserves all rights to declare any of its data confidential or of business importance and will provide it only to the regulatory authorities of concern on request/demand.

Publications except for summaries of product characteristics are subject to the written consent of the other party of the contract, which shall not unduly be refused.

## 16. INVESTIGATOR AGREEMENT

I have read and understand the protocol (including the Summary of Product Characteristics for Medabon) and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed of the requirements of the protocol, the data collection methods and the conduct of the study in general. I am aware that this protocol may be approved by the Ethics Committee (EC) responsible for such matters in the Clinical Study Facility prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this EC approved protocol will be submitted to the European Medicines Agency (EMA) and other regulatory authorities by the sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilised by the sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor monitors and auditors full access to all medical records at the research facility for subjects screened or entered into the registry.

I agree to provide all subjects with informed consent forms, as required by government laws and ICH regulations. I further agree to report to the sponsor any adverse experiences in accordance with the terms of this protocol, and ICH guideline, Part E6, Section 4.11.

Principal Investigator

Date

## **17. REFERENCES**

Ashok PW, Penney GC, Flett GMM, and Templeton A. An effective regimen for early medical abortion: A report of 2000 consecutive cases. Hum Reprod 1998; 13: 2962-2965.

Honkanen H, Piaggio G, von Hertzen H, et al.WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion II: Side-effects and women's perceptions. BJOG 2004; 111: 715-725.

RCOG, Royal College of Obstetricians and Gynaecologists. (Revised November 2011) The care of women requesting induced abortion: Evidence-based guideline No7. London, RCOG Press.

von Hertzen H, Honkanen H, Piaggio G, et al. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I. Efficacy. BJOG 2003; 110(9): 808-818.

von Hertzen H, Piaggio G, Huong NT, et al. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomized controlled equivalence trial. Lancet 2007; 369: 1938-1946.

von Hertzen H, Huong NT, Piaggio G, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled non-inferiority trial. BJOG 2010; 117: 1186-1196.

Warriner IK, Wang D, Huong NT, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomised controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-1161.

World Health Organization (WHO), Task Force on Post-ovulatory Methods of Fertility Regulation. Termination of pregnancy with reduced doses of mifepristone. BMJ 1993; 307: 532-537.

World Health Organization (WHO), Task Force on Post-ovulatory Methods of Fertility Regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: A randomised trial. BJOG 2000; 107: 524-530.

World Health Organization (WHO), Task Force on Post-ovulatory Methods of Fertility Regulation. Medical abortion at 57 to 63 days" gestation with a lower dose of mifepristone and gemeprost: A randomised controlled trial. Acta Obstet Gynaecol Scand 2001; 80: 447-451.

WHO study A35148: Comparison of two doses and two routes of administration of misoprostol after pre-treatment with mifepristone for early pregnancy termination.

WHO study 97903: A double-blind, randomised, controlled multicentre trial of three misoprostol regimens after pre-treatment with mifepristone for termination of early pregnancy.

WHO study A65037: A comparative pharmacokinetic study of oral mifepristone and vaginal misoprostol in pregnant women.

Tang OS, Chan CCW, Ng EHY, et al. 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; 18: 2315-2318.

Shannon C, Brothers LP, Philip, NM and Winikoff B. Infection after medical abortion: A review of the literature. Contraception 2004; 70: 183-190.
## **APPENDIX 1 - CAUSALITY ASSESSMENTS FOR ADVERSE EVENTS**

## **Study Drug Causality**

The relationship of an AE to study treatment will be assessed with consideration to the following criteria:

- Temporal relationship to the initiation of study medication
- Response of the event to withdrawal of study medication
- AE profile of concomitant therapies
- Clinical circumstances during which the AE occurred
- Subject"s clinical condition and medical history

Categorization\* of causality will be designated by the investigator as stated below:

- <u>Unrelated</u> this category applies to AEs that are clearly due to causes other than the study medication.
- <u>Unlikely related</u> this category applies to AEs for which there is no reasonable evidence or argument to suggest a causal relationship between the study medication and the AE.
- **<u>Possibly related</u>** this category applies to AEs for which there is reasonable evidence or argument to suggest a causal relationship between the AE and the study medication.
- **Definitely related** this category applies to AEs that are considered to be related to the study medication, with a high degree of certainty

\* For the purposes of regulatory reporting, categories "possibly related" and "definitely related" will be considered "related".

APPENDIX 2 – EUROPEAN SUMMARY OF PRODUCT CHARACTERISTICS

## **Concept Foundation**

111 Paholyothin Rd., Thailand Science Park Klong 1, Klong Luang Pathumthani 12120 THAILAND www.conceptfoundation.org

## lpas

P. O. Box 5027 Chapel Hill, NC 27514 USA www.ipas.org

## PATH

1455 NW Leary Way Seattle, WA 98107 USA www.path.org

This material may be adapted and distributed for nonprofit or educational purposes without obtaining permission. Please credit the Concept Foundation, lpas, and PATH as the source of these materials.







## **Concept Foundation**

111 Paholyothin Rd., Thailand Science Park Klong 1, Klong Luang Pathumthani 12120 THAILAND www.conceptfoundation.org

## lpas

P. O. Box 5027 Chapel Hill, NC 27514 USA www.ipas.org

## PATH

1455 NW Leary Way Seattle, WA 98107 USA www.path.org

This material may be adapted and distributed for nonprofit or educational purposes without obtaining permission. Please credit the Concept Foundation, lpas, and PATH as the source of these materials.









Medical and Service Delivery Guidelines

## Medabon®: Medical and Service Delivery Guidelines

## Contents

## **SECTION 1**

Background information on Medabon®

## SECTION 2

Screening for Medabon®

## SECTION 3

Prescribing and administering Medabon®

## SECTION 4 Following up

#### REFERENCES

#### **RELATED RESOURCES**

These guidelines represent a consensus view of three agencies for the Medabon<sup>®</sup> product that may differ from their own general medical abortion protocols.

This document can be found online at www.medabon.info. To request additional copies, please contact Concept Foundation at medabon@conceptfoundation.org. Medabon<sup>®</sup> is a combination therapy for medical abortion in pregnancies through nine weeks, or up to and including 63 days since a woman's last menstrual period (LMP). Medical abortion refers to the process of ending a pregnancy by taking medication, rather than through surgical intervention.<sup>\*</sup> It may also be referred to as medication abortion, the abortion pill, non-aspiration abortion, or non-surgical abortion. The term "medical abortion" does not mean that a physician needs to be involved or that the procedure is performed out of medical necessity.

Medical abortion has been used by millions of women throughout the world. In 2006, the World Health Organization (WHO) released updated recommendations on medical abortion based on available evidence.<sup>1</sup> According to these recommendations, medical abortion through nine weeks' gestation is safe and effective. The most effective and safest medical abortion regimen requires the use of two drugs, mifepristone and misoprostol. Medabon<sup>®</sup> packages contain mifepristone and misoprostol together.

This document on Medabon<sup>®</sup> has four sections that roughly correspond to the medical abortion process from a health worker's perspective: background information, screening, administration, and followup. The protocol on page 9 provides an overview of the medical abortion process using Medabon<sup>®</sup>. This document was developed for an audience with a moderate amount of medical expertise. The level of technical detail and language may be adapted for the health providers who will be implementing services in a specific setting.

\* The term "surgical abortion" is often used to refer to procedures such as vacuum aspiration (electric or manual) and sharp curettage, also known as dilatation and curettage (D&C).

## Background information on Medabon®

Mifepristone and misoprostol are licensed separately in many countries. Medabon<sup>®</sup> offers the benefit of the drugs being licensed and packaged together in one medical abortion product.



Mifepristone acts by blocking progesterone receptors, leading to changes in the endometrial lining so that it ceases to support pregnancy, softening and dilation of the cervix, and increased uterine sensitivity to prostaglandins (such as misoprostol).<sup>2</sup>

Misoprostol is the preferred prostaglandin analog for use with mifepristone because of its efficacy, safety, low cost, and wide availability.<sup>3</sup> Misoprostol softens the cervix and increases uterine contractility, and the contractions expel the pregnancy.

## **Dosing and regimen**

The Medabon® regimen consists of one 200-mg tablet of mifepristone given orally, followed one to two days (24 to 48 hours) later by four 200-µg tablets of misoprostol. This is the regimen recommended by WHO as a safe and effective method for medical abortion.<sup>1</sup>

## Misoprostol administration

Women have options in terms of when and how they can take misoprostol.\* Providers should discuss these options with each woman taking Medabon<sup>®</sup> so that she can choose the regimen most optimal to her needs and preferences.

## **MISOPROSTOL** administration

(Day 1 is mifepristone day)

Route	Timing
Vaginal (800 µg)	Day 2 or 3
Sublingual (800 µg)	(24–48 nours after mifepristone)

Medabon® is registered for vaginal and sublingual use of misoprostol. See page 8 for complete instructions regarding administration of misoprostol, including through vaginal and sublingual routes. There is additional evidence that buccal use of misoprostol (i.e., inserting pills between the cheek and the gum) is also effective and is widely used in some countries,<sup>8–10</sup> but Medabon® is not currently labeled for this route.

Medical abortion with Medabon<sup>®</sup> generally requires three steps:

- 1 Administration of mifepristone.
- 2 Administration of misoprostol one to two days later.
- **3** A follow-up assessment one to two weeks (generally 10–14 days) after mifepristone administration to confirm completion of abortion.

\* The initial registrations and labeling for Medabon<sup>®</sup> recommended that misoprostol be used vaginally 36–48 hours after mifepristone. Since then, Concept Foundation has gained access to data showing that misoprostol can be administered safely and effectively by the sublingual route,<sup>4,5</sup> and misoprostol can be administered by both the vaginal and sublingual routes 24–48 hours post-mifepristone.<sup>6,7</sup> These changes are being made to regulatory submissions and eventually to packaging materials. Despite this original labeling, providers may wish to comply with the new evidence-based regimens stated in these guidelines.

## Effectiveness

An effective medical abortion is generally defined as a pregnancy terminated without need for another uterine evacuation method, such as vacuum aspiration or curettage. The Medabon® regimen has been shown to achieve complete abortion in about 98 percent of cases, and less than 1 percent of women using this regimen experience ongoing, viable pregnancies.<sup>5,11</sup>

The rate of complete abortion for the Medabon<sup>®</sup> regimen can vary by provider. As provider experience increases, they are likely to be more comfortable with the method and less likely to perform unnecessary interventions. Following the regimen outlined in these guidelines will help ensure the highest rates of success. For example, adhering to the suggested interval between administration of misoprostol and a follow-up visit will help ensure that a woman's abortion has had time to complete and will make unnecessary intervention less common. Of course, women should seek follow-up care sooner if they have problems or concerns.

## **Expected effects**

Vaginal bleeding and cramping are normal and expected. The medical abortion process may feel like an intense, crampy, and long menstrual period, or similar to a spontaneous miscarriage.

Vaginal bleeding, often accompanied by the passage of clots, is usually heavier than a menstrual period. Bleeding sometimes begins after taking mifepristone, but most often starts one to three hours after misoprostol is taken. The amount and duration of bleeding varies: bleeding is generally heaviest for a few hours during the actual abortion and has the general pattern of diminishing over time, often lasting up to two to three weeks. Cramping is typically strongest in the hours after misoprostol is taken, then eases off after the pregnancy is expelled.<sup>12</sup>

After the pregnancy passes, which the woman may not be able to differentiate from other blood and/or clots, she will likely experience a persistent decrease of bleeding and cramps until the bleeding ends.

## Side effects

Uterine contractions can be painful, and some women will experience side effects—including nausea, vomiting, diarrhea, headache, chills, shivering, and transient fever lasting less than a day. There are no long-term health effects of Medabon®, nor will the medication impact any future pregnancies.<sup>13</sup>

### Medabon<sup>®</sup> key facts

- Medabon<sup>®</sup> consists of two medicines: mifepristone and misoprostol.
- The Medabon<sup>®</sup> regimen is in line with current (as of June 2009) WHO recommendations for medical abortion<sup>1</sup>: one 200-mg tablet of mifepristone given orally, followed 24–48 hours later by four 200-µg tablets of misoprostol. The four misoprostol tablets can be administered vaginally or sublingually.
- Medabon® is registered for use in pregnancies through nine weeks (63 days) since a woman's LMP.
- Medical abortion with mifepristone and misoprostol has been shown to be 98 percent effective when used through nine weeks (63 days) since LMP.<sup>5</sup>

# **2** Screening for Medabon<sup>®</sup>

## Contraindications

There are very few situations that absolutely exclude a woman from taking Medabon<sup>®</sup>.

## Women cannot take Medabon® if they:

- Are allergic to any of the drugs involved (mifepristone, misoprostol, or another prostaglandin).
- Have inherited porphyria, a rare blood disorder.<sup>14</sup>
- Have a hemorrhagic disorder or are on concurrent anticoagulant therapy, unless transfusion services are available (there is very limited evidence describing provision of medical abortion in such cases).
- Have a known or suspected ectopic pregnancy.

## **Precautions**

## Women with these conditions should be treated with caution specific to their situation:

- Currently taking long-term systemic corticosteroid therapy for asthma or other conditions.<sup>15,16</sup> By contrast, the medicines in asthma inhalers are not systemically absorbed and women taking these medicines may use Medabon<sup>®</sup>.
- Chronic adrenal failure. It is possible that women with chronic adrenal failure may acutely develop dehydration, low blood pressure, or shock after taking mifepristone. Women with chronic adrenal failure should take an increased dose of glucocorticoids when using mifepristone and should be carefully monitored for signs and symptoms of shock.<sup>15,16</sup>

**Note:** Women with multiple gestation<sup>17</sup> and obese women<sup>18</sup> may be given Medabon<sup>®</sup> in the same doses as other women. Additionally, women who have used Medabon<sup>®</sup> in the past may use it again with no decrease in efficacy.

## **Special considerations**

There is little evidence on the use of medical abortion in women with the following conditions: severe anemia (hemoglobin level < 9 g/dL), clinical illness or unstable health problems, or sepsis. Whether to administer medical abortion to women with these conditions will depend on the available options for safe abortion care, referrals, and clinical judgment.

The following women can take Medabon<sup>®</sup>, but may require additional information or clinical care:

- Women who are breastfeeding. Misoprostol enters breast milk soon after administration, and it is likely that mifepristone does as well. There is no evidence to suggest that either medication is harmful to infants. Women who are concerned about the effects of misoprostol on infants can take the medication immediately after nursing.<sup>19</sup>
- Women with an intrauterine device (IUD). Women with an IUD can be treated with Medabon<sup>®</sup> as long as the IUD is removed beforehand. See page 11 for information on reinitiating contraception after taking Medabon<sup>®</sup>.
- Women with sexually transmitted infections (STIs). Women with a confirmed STI should be treated concurrently with the initiation of medical abortion. Women with a suspected STI should be evaluated or referred and treated as appropriate for the health care setting; however, treatment of suspected STIs should not delay the abortion.

Given that Medabon<sup>®</sup> is only licensed for pregnancies through nine weeks, the likelihood of Rh-sensitization is very low. There is currently not enough evidence to recommend for or against Rh screening through nine weeks since LMP.<sup>20</sup> Depending on the prevalence of RhD-negative blood in the population and the ability to offer Rh-immune globulin, the country standard should be followed.

## Confirming pregnancy and timing

Medabon<sup>®</sup> is licensed for women with pregnancies through nine weeks: in other words, a woman can take Medabon<sup>®</sup> through 63 days after the first day of her LMP.

Duration of pregnancy can generally be confirmed by taking the woman's history and with a physical examination. If signs of pregnancy are not clearly present, a blood or urine test confirming pregnancy may be required. Ultrasound is not necessary and should not be a prerequisite for abortion in settings where it is unavailable or makes the procedure overly expensive.<sup>1,21</sup> Where ultrasound is available, it may help to determine the length of pregnancy in cases of a discrepancy in dating, or to confirm an intrauterine pregnancy.

## Choosing medical abortion or vacuum aspiration

Both medical abortion and vacuum aspiration have been found to be acceptable methods to women.<sup>22,23,24</sup> Women are more likely to find a method acceptable if they have chosen it themselves.<sup>25,26</sup>

Women choose medical abortion or vacuum aspiration for a variety of reasons that reflect a woman's specific circumstances and cultural context. Factors women consider in choosing between available methods include the length of gestation, the duration of the abortion process, where the abortion will occur, and what they are likely to experience.<sup>23</sup>

Both medical abortion and vacuum aspiration are safe and effective methods with low complication rates.<sup>11,27</sup> There are, therefore, very few situations where a clear medical preference for either method exists.

## Undiagnosed ectopic pregnancy

An ectopic pregnancy is a pregnancy located outside the uterine cavity. Medabon® does not treat ectopic pregnancy, a preexisting condition rather than a complication of the abortion procedure. Therefore, ectopic pregnancy may be diagnosed when a woman seeking a medical abortion undergoes clinical assessment before the procedure. However, ectopic pregnancy can go undetected during clinical assessment and even remain undetected after a medical abortion is performed. A woman may still experience bleeding and cramping after taking Medabon<sup>®</sup>, even if she has an ectopic pregnancy, and a provider is unlikely to examine the expelled tissue to confirm termination of pregnancy. Therefore, diagnosis and treatment of ectopic pregnancy may take place in the course of follow-up.

Typical symptoms of ectopic pregnancy are abdominal or pelvic pain—often one-sided and vaginal bleeding. Pain and bleeding may be persistent or erratic and variable and, in some cases, absent.<sup>28</sup> High-risk factors for ectopic pregnancy are tubal surgery, tubal sterilization, previous ectopic pregnancy, in utero exposure to diethylstilbestrol, use of intrauterine device (IUD)\*, and documented tubal disease.<sup>30</sup>

Ectopic pregnancy can sometimes be confirmed with an ultrasound, but often an ultrasound can only confirm the absence of an intrauterine pregnancy. With serial  $\beta$ -hCG measurements *and* ultrasound showing an empty uterine cavity in an asymptomatic patient, ectopic pregnancy can be strongly suspected. It is rare to actually see the ectopic pregnancy on ultrasound, unless a very good unit, a transvaginal probe, or a highly skilled sonographer is available and the patient's pelvic anatomy and location of the ectopic pregnancy permit visualization. If ultrasound is not available and ectopic pregnancy is suspected, or if the woman is symptomatic for ectopic pregnancy, she should be referred to an appropriate gynecology service for urgent treatment.

\* Women with an IUD in place and those who have had tubal ligation are more likely to have an ectopic than intrauterine pregnancy if conception does occur, but their baseline risk of pregnancy is far lower than that of women not using contraception.<sup>29</sup>

Possible reasons to recommend **medical abortion**:

- Severe obesity. A surgical procedure may be more technically challenging.<sup>1</sup>
- Uterine malformations, a fibroid uterus, or previous cervical stenosis.
- A wish to avoid an invasive procedure.

Possible reasons to recommend **surgical abortion** (usually vacuum aspiration):

- Contraindications to medical abortion.
- Time or geographical constraints preclude follow-up to confirm that medical abortion is complete.
- A woman has made the free and informed choice that she would like to be sterilized or have an IUD inserted, and the procedures can be carried out at the same time.
- Suspected ectopic pregnancy (so tissue can be examined to verify complete abortion).

Each woman who chooses medical abortion should be clearly informed:

- What will be done at each visit and what she will experience or do at home.
- What the medical abortion may feel like.
- What the common side effects are.
- How long the process may take.
- What the potential risks and complications are.
- What pain medications are available and how to use them.
- That she must plan to complete the abortion process once she starts it.
- When she will be able to resume her normal activities, including sexual intercourse.
- When she needs to seek medical attention.
- What contraceptive methods are available and how to get/start them.



## Prescribing and administering Medabon<sup>®</sup>

## Scheduling medical abortion with Medabon®

The full medical abortion process should be taken into consideration when health providers and women schedule clinic visits. For most women, expulsion will happen within four to six hours of taking misoprostol.<sup>31</sup> Bleeding and cramping will likely be heaviest at this time. If misoprostol is administered in a clinic setting, it is advisable that a woman stays in the clinic until she feels comfortable and able to return home. Women should be informed of this in advance so that they can plan for misoprostol administration around travel time, work and family needs, and the ability to have someone there with her if she chooses.

Women should have access to emergency care during the medical abortion process. Providers and women should make a plan for where to seek emergency care in the rare event of a serious complication.

## Medabon® administration

- **Step 1.** Woman swallows one mifepristone pill. If a woman vomits within 30 minutes of taking mifepristone, she will need to take another mifepristone pill.
- **Step 2.** Four 200-μg misoprostol tablets are administered one or two days (24–48 hours) later (see box "Misoprostol administration," page 3).

*Vaginal administration:* The woman or health worker should use their finger to push the four tablets one at a time into the vagina as far as they are able.

Health workers who administer misoprostol vaginally should follow the instructions on the package insert and wear clean gloves. If women administer misoprostol vaginally themselves, either at home or in the clinic, they should be advised to wash their hands first. Sublingual administration: Women should place two tablets of misoprostol under their tongue and wait for them to dissolve. As soon as they have dissolved, two more tablets can be taken in the same way. If the first two tablets have not dissolved after 20 minutes, women can swallow any remaining fragments and take the final two tablets.

Some women may prefer to take all four tablets at once. In that case, women should place all four tablets under the tongue and wait for them to dissolve. If they have not dissolved after 20 minutes, women can swallow any remaining fragments.

Swallowing the tablets whole (oral administration) is less effective than placing them under the tongue until they dissolve or for 20 minutes.<sup>5</sup>

More information on **Step 3**, the follow-up visit, is provided on page 12.

## **Resuming normal activities**

Women should have clear expectations regarding when they will or can resume normal activities. For example:

- Showering and bathing are fine at any time in the medical abortion process. Vaginal douching is not recommended.<sup>32</sup>
- Women may ask when they are able to resume sexual activity. There is no evidence base to suggest ideal timing, but women should be encouraged to wait until they feel comfortable and ready (see below).
- Women can ovulate, and therefore get pregnant, before menstruation returns to normal. Women who want to prevent pregnancy should use a contraceptive method during sexual relations after taking Medabon<sup>®</sup>.
   Women have been found to ovulate as early as ten days following abortion. See page 11 for more information about contraceptive options.
- The return of menses following medical abortion will generally occur after about five weeks.<sup>33</sup>

## Medabon® Clinic Visits and Protocol

#### **STEP 1** Initial clinic visit and mifepristone administration

- Confirm pregnancy and length of pregnancy.
- Counsel woman on pregnancy/abortion options.
- · Complete physical exam and medical history.
- Screen for contraindications and risk factors.
- Rule out ectopic pregnancy.

## For women who choose Medabon<sup>®</sup> and will take misoprostol **in the clinic:**

- Counsel woman on what to expect.
- Create schedule of Medabon<sup>®</sup> visits.
- Create plan for emergency follow-up care.
- Provide suggestions for dealing with side effects.
- Woman takes mifepristone orally.

For women who choose Medabon<sup>®</sup> and will take misoprostol **at home:** 

- Counsel woman on how to administer misoprostol vaginally or sublingually, using visual aids as appropriate.
- Review signs of serious complications and confirm woman has printed materials.
- Create plan for emergency follow-up care.
- Provide suggestions for dealing with side effects and make pain medication available.
- Schedule follow-up visit.
- Provide misoprostol tablets to take home.
- Woman takes mifepristone orally.

#### **STEP 2** Misoprostol administration (24–48 hours later)

### In the clinic:

- Administer misoprostol vaginally or sublingually.
- Make pain medication available.
- Review signs of serious complications and confirm woman has printed materials.
- Review plans for follow-up visit.
- Review side effects and management.

#### At home:

• Woman administers misoprostol vaginally or sublingually.

## Contraception

Discuss contraceptive options early in the process.

The woman's choice of method will determine when contraception is provided.

#### **STEP 3** Follow-up visit (10–14 days after mifepristone administration)

- Confirm that abortion is successful (most women will be in this category).
- If the woman is experiencing problematic bleeding (see page 12 for more detail), treatment options include:
  - Waiting longer for bleeding to stop.
  - An additional dose of misoprostol.
  - Uterine evacuation.
- In the case of continuing pregnancy, uterine evacuation is recommended.

## Managing effects of the abortion

### Bleeding

Bleeding can be managed similarly to a very heavy menstrual period or a spontaneous miscarriage (e.g., with sanitary pads or cotton wool). It will be heaviest after taking misoprostol—often during expulsion of the products of conception—and light bleeding may last two weeks or longer. It is not uncommon for bleeding to stop and then start again. Some women, up to 20 percent in one study, may continue to have bleeding or spotting 35–42 days after the initiation of a medical abortion.<sup>34</sup> If bleeding is heavy, prolonged, or causes anemia (or symptoms of anemia, such as dizziness, faintness, or significant loss of energy), then vacuum aspiration, fluid replacement, or transfusion might be required. The risk of bleeding requiring intervention (transfusion and/or aspiration) ranges from 0.02 to 1.8 percent.35-37

### Cramping and pain

Women are most likely to feel pain in the first few hours after administration of misoprostol.<sup>1</sup> Women should receive medicines (or where they are unavailable, prescriptions or recommendations for medicines) to manage pain and have the pain medicine available when taking the misoprostol. Nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen (400–800 mg) have been shown to be more effective than paracetamol (500–1,000 mg)<sup>38</sup> and can be taken at the same time as misoprostol, but not before. If possible, women should have access to or at least a prescription for a narcotic pain medicine in the event they need it; codeine 30–40 mg may be added to either NSAIDs or paracetamol. Women should be advised of other comfort measures, such as use of hot water bottles.

## Seeking care for possible complications

When educating women about the use of Medabon<sup>®</sup>, it is important to stress that serious complications are rare, but that they should be on the look-out for the following signs and symptoms, and seek help (ideally from their original provider) if they experience:

- Persistent, heavy bleeding to the point where they feel sick or weak, or if they soak more than two pads per hour for more than two consecutive hours.
- Fever of 38°C/100.4°F or higher continuing for more than the day following misoprostol use.
- Persistent vomiting or diarrhea for more than the day on which misoprostol was administered.
- Very severe, continuous, or increasing abdominal pain that is unrelieved by medication, rest, a hot water bottle, or a heating pad.

Little to no bleeding 24–48 hours following misoprostol is not an emergency, but is cause for seeking follow-up care as it may be a sign of continued pregnancy.

Infection after medical abortion procedures is rare. Women should, however, be informed of the symptoms of infection and encouraged to seek follow-up care should symptoms of infection occur. The severity of the infection should determine what treatment is provided; oral antibiotics are used for most treatment of infection or presumed infection.<sup>39</sup>

Women should always be given printed information on signs of complications to take home (see the sample patient brochure in these materials). As noted previously, providers and women should discuss a plan for emergency care prior to the medical abortion process. Ideally, women should seek care for complications from their original providers. If the original provider is not available, accessible, or cannot provide the necessary follow-up, providers should work with women to identify an alternative in advance. Women should be encouraged to take their informational materials with them if they seek emergency care elsewhere, in case the facility is unfamiliar with medical abortion and associated complications. Most back-up care is similar to that needed by women having a spontaneous abortion, and many communities have a health care facility already in place to provide such care. In rare cases, serious complications do occur that require emergency follow-up (see the "Medical Guidelines for Providers of Emergency Care" included in this packet).

## **Contraceptive counseling and services**

Women taking Medabon<sup>®</sup> should be offered contraception. Women can become pregnant within ten days of the abortion if they are not using an effective method of contraception.<sup>40</sup> Evidence supports the use of any modern contraceptive method after an uncomplicated abortion.<sup>41,42</sup>

Women can begin taking hormonal methods, whether combined (estrogen and progestin) or progestin-only, on the same day as misoprostol administration, when expulsion of the products of conception generally occurs.<sup>43</sup> These methods include oral contraceptives,<sup>44–46</sup> injectable methods, implants, and the contraceptive patch. For women taking the misoprostol at home, they can be given any patient-initiated hormonal methods and told to start them on the day they take misoprostol. They may see a provider for injectable contraception or implants. The vaginal contraceptive ring can be started when bleeding slows down after expulsion of the pregnancy. Condoms, spermicides, the cervical cap, and the diaphragm can be used as soon as women start having sex again.<sup>1</sup> If a woman would like to have an IUD inserted or undergo sterilization, these procedures should be performed after an assessment confirms that the woman is no longer pregnant and the products of conception have been expelled.

Natural family planning or fertility-awareness methods cannot be initiated until a woman's regular cycles have resumed, and she may need to use a barrier method like a condom or a diaphragm—in the meantime.

# 4 Following up

A follow-up visit is desirable approximately two weeks (10–14 days) after taking Medabon<sup>®</sup>. During this visit, the clinician confirms that the woman is no longer pregnant and that bleeding patterns are within the expected range, ensures contraception is provided if desired, and answers her questions. Confirmation that the pregnancy has been terminated is possible by pelvic examination, bleeding and symptom history, or by ultrasound, if necessary.

The following scenarios represent the most likely situations encountered at the follow-up visit:

## Successful medical abortion

The woman reports she no longer feels pregnant, has taken the medications as instructed, and had bleeding and cramping consistent with a successful medical abortion. This is the most common outcome.

## **Problematic bleeding**

Problematic bleeding encompasses a range of bleeding patterns that may be tiresome or problematic for the woman, or, in rare cases, are true emergencies. In the case of problematic bleeding, the pregnancy is not growing, but the woman's bleeding pattern is not gradually diminishing. The pelvic exam is consistent with a small or non-pregnant uterus. Treatment options, unless indicated otherwise below, are: 1) waiting longer for bleeding to stop; 2) an additional dose of misoprostol, which may help the uterus contract and expel residual tissue or a persistent empty sac; or 3) uterine evacuation.

Various patterns of problematic bleeding requiring specific interventions are:

• Persistently heavy bleeding. The woman may have been bleeding continuously—like during a heavy menstrual period—since she took misoprostol. If the woman feels weak from bleeding, a uterine aspiration is recommended. If she is clinically stable and feels well, a repeat dose of misoprostol may be offered as long as the woman is willing and able to return two days to one week later, depending on the duration and amount of problematic bleeding, to assess whether bleeding is diminishing.<sup>45</sup> Although providing a second dose of misoprostol is a practice used by some providers to increase uterine contractility and expel residual tissue, its use has been studied for expulsion of a persistent sac or unexpelled embryo<sup>47</sup>; providing a repeat dose of misoprostol has not been studied for alleviation of problematic bleeding.

- Erratic bleeding. Some women have days of very little bleeding, no bleeding, or spotting, and erratically experience very heavy, gushing bleeding. If a woman is symptomatic for anemia, perform uterine aspiration.
- Hemorrhage. Hemorrhage causing hemodynamic instability is an emergency and is treated with an immediate uterine evacuation to empty the uterus. If the hemorrhage has been very serious, blood or fluid transfusion should be considered. If transfusion services are not available, the woman should be transported to the nearest facility providing these services.

## **Continued pregnancy**

The woman reports continued pregnancy symptoms and the uterus is larger than on previous exam. Uterine evacuation is recommended at this time.

## Possible birth defects if pregnancy continues

Evidence on birth defects associated with mifepristone or misoprostol are inconclusive. From an estimated two million procedures performed between 1987 and 2008 in countries where Exelgyn Laboratories holds marketing authorization for a mifepristone product—Mifegyne®—a total of 26 malformations have been reported in cases where the combined treatment failed or the woman changed her mind about the procedure after taking the mifepristone.<sup>48</sup> Six cases of malformation have been reported after use of mifepristone alone, and twenty other cases have been reported after use of mifepristone and a prostaglandin. According to these authors, none of the events have been conclusively related to the treatment.

Women who choose to carry a pregnancy to term should be counseled on the possibility of birth defects and encouraged to seek active follow-up care throughout pregnancy.

## References

- 1 World Health Organization (WHO). Frequently Asked Questions about Medical Abortion: Conclusions of an International Consensus Conference on Medical Abortion in Early First Trimester, Bellagio, Italy. Geneva: WHO; 2006. Available at: www.who.int/ reproductive-health/publications/medical\_abortion/.
- 2 Creinin M. Medical abortion regimens: historical context and overview. *American Journal of Obstetrics & Gynecology*. 2000;(2Suppl):S3–S9.
- 3 Foster A. Medication Abortion: A Guide for Health Professionals. Cambridge: Ibis Reproductive Health; 2005. Available at: www.ibisreproductivehealth.org/downloads/Medication\_ abortion\_A\_guide\_for\_health\_professionals\_English.pdf.
- 4 Tang OS, Chan C, Ng E, Lee S, Ho P. 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. *Human Reproduction*. 2003;18(11):2315–2318.
- Raghavan S, Comendant R, Digol I, et al. Two-pill regimens of misoprostol after mifepristone medical abortion through 63 days' gestational age: a randomized controlled trial of sublingual and oral misoprostol. *Contraception*. 2009; 79(2):84–90.
- 6 Hamoda H, Ashok PW, Dow J, Flett GM, Templeton A. A pilot study of mifepristone in combination with sublingual or vaginal misoprostol for medical termination of pregnancy up to 63 days gestation. *Contraception*. 2003;68(5):335–338.
- von Hertzen H, Piaggio G, Wojdyla D, et al. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomized factorial controlled equivalence trial. *British Journal of Obstetrics and Gynaecology.* 2009;116(3):381–389.
- 8 Winikoff B, Dzuba IG, Creinin MD, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstetrics & Gynecology*. 2008;112(6):1303–1310.
- Fjerstad M, Sivin I, Lichtenberg ES, Trussel J, Cleland K, Cullins V. Effectiveness of medical abortion with mifepristone and buccal misoprostol through 59 gestational days. *Contraception*. In press.
- 10 Middleton T, Schaff E, Fielding S, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception*. 2005;72(5):328–332.

- 11 Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. Factors affecting the outcome of early medical abortion: a review of 4132 consecutive cases. *British Journal of Obstetrics and Gynaecology*. 2002;109(11):1281–1289.
- 12 Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. *New England Journal of Medicine*. 1998;338(18):1241–1247.
- 13 Virk J, Zhang J, Olsen J. Medical abortion and the risk of subsequent adverse pregnancy outcomes. *New England Journal of Medicine*. 2007;357:648–653.
- 14 Cable EE, Pepe JA, Donohue SE, Lambrecht RW, Bonkovsky HL. Effects of mifepristone (RU-486) on heme metabolism and cytochromes P-450 in cultured chick embryo liver cells, possible implications for acute porphyria. *European Journal of Biochemistry*. 1994;225(2):651–657.
- Sitruk-Ware R. Mifepristone and misoprostol sequential regimen side effects, complications and safety. *Contraception*. 2006;74(1):48–55.
- 16 Davey A. Mifepristone and prostaglandin for termination of pregnancy: contraindications for use, reasons and rationale. *Contraception*. 2006;74(1):16–20.
- 17 Hayes JL, Achilles S, Reeves MF, Creinin MD. Outcomes of medical abortion through 63 days in women with twin gestations. *Contraception*. 2008;78(2):168–169.
- Strafford M, Mottl-Santiago J, Savla A, Soodoo N, Borgatta L. Relationship of obesity to outcome of medical abortion. *American Journal of Obstetrics & Gynecology*. 2009;200(5): e34–36.
- 19 Vogel D, Burkhardt T, Rentsch K, et al. Misoprostol versus methylergometrine: pharmacokinetics in human milk. *American Journal of Obstetrics & Gynecology*. 2004;191(6): 2168–2173.
- Fiala C, Fux M, Gemzell-Danielsson K. Rh-prophylaxis in early abortion. *Acta Obstetricia et Gynecologica Scandinavica*. 2003;82(10):892–903.
- 21 World Health Organization (WHO). *Safe Abortion: Technical and Policy Guidance for Health Systems*. Geneva: WHO; 2003. Available at: www.who.int/reproductive-health/publications/ safe\_abortion/.

- 22 Creinin, MD. Randomized comparison of efficacy, acceptability and cost of medical versus surgical abortion. *Contraception*. 2000;62(3):117–124.
- 23 Winikoff B, Irving S, Kurus J, et al. Safety, efficacy, and acceptability of medical abortion in China, Cuba, and India: a comparative trial of mifepristone-misoprostol versus surgical abortion. *American Journal of Obstetrics & Gynecology*. 1997;176(2):431–437.
- 24 Tang OS, Miao BY, Lee SW, Ho PC. Pilot study on the use of repeated doses of sublingual misoprostol in termination of pregnancy up to 12 weeks gestation: efficacy and acceptability. *Human Reproduction*. 2002;17(3):654–658.
- 25 Henshaw RC, Naji SA, Russell IT, Templeton AA. Comparison of medical abortion with surgical vacuum aspiration: women's preferences and acceptability of treatment. *British Medical Journal*. 1993;307(6906):714–717.
- 26 Slade P, Heke S, Fletcher J, Stewart P. A comparison of medical and surgical termination of pregnancy: choice, emotional impact and satisfaction with care. *British Journal of Obstetrics and Gynaecology*. 1998;105(12):1288–1295.
- 27 Hakim-Elahi E, Towell HM, Burnhill MS. Complications of first trimester abortion: a report of 170,000 cases. *Obstetrics & Gynecology*. 1990;76(1):129–135.
- 28 Seeber B, Barnhart K. Suspected ectopic pregnancy. Obstetrics & Gynecology. 2006;107:399–413.
- 29 Rossing M, Daling J, Voigt L, Stergachis A, Weiss N. Current use of an intrauterine device and risk of tubal pregnancy. *Epidemiology*. 1993;4(3):252–258.
- 30 Pisarka M, Carson S, Buster J. Ectopic pregnancy. *The Lancet*. 1998;351:1115.
- El-Refaey H, Templeton A. Early induction of abortion by a combination of oral mifepristone and misoprostol administered by the vaginal route. *Contraception*. 1994;49(2):111–114.
- **32** Tsai CS, Shepherd BE, Vermund SH. Does douching increase risk for sexually transmitted infections? A prospective study in high-risk adolescents. *American Journal of Obstetrics & Gynecology*. 2009;200(1):38.e1–8.
- **33** World Health Organization Task Force on Post-ovulatory Methods for Fertility Regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomized trial. *British Journal of Obstetrics and Gynaecology*. 2000;107(4):524–530.
- 34 Davis A, Westhoff C, De Nonno L. Bleeding patterns after early abortion with mifepristone and misoprostol or manual vacuum aspiration. *Journal of the American Medical Women's Association*. 2000;55(3Suppl):141–144.

- 35 Ashok PW, Penney GC, Flett GM, Templeton A. An effective regimen for early medical abortion: a report of 2000 consecutive cases. *Human Reproduction*. 1998;13(10): 2962–2965.
- 36 Hausknecht R. Mifepristone and misoprostol for early medical abortion: 18 months experience in the United States. *Contraception*. 2003;67(6):463–465.
- 37 Schaff E, Stadalius L, Eisinger S, Franks P. Vaginal misoprostol administered at home after mifepristone (RU486) for abortion. *Journal of Family Practice*. 1997;44(4):353–361.
- 38 Livshits A, Machtinger R, David LB, Spira M, Moshe-Zahav A, Seidman DS. Ibuprofen and paracetamol for pain relief during medical abortion: a double-blind randomized controlled study. *Fertility and Sterility*. 2009;91(5):1877–1880.
- 39 Shannon C, Brothers LP, Philip NM, Winikoff B. Infection after medical abortion: a review of the literature. *Contraception*. 2004;70(3):183–190.
- 40 Boyd EF Jr, Holmstrom EG. Ovulation following therapeutic abortion. *American Journal of Obstetrics & Gynecology*. 1972;113(4):469–473.
- **41** Mittal S. Contraception after medical abortion. *Contraception*. 2006;74(1):56–60.
- **42** World Health Organization (WHO). *Medical eligibility criteria for contraceptive use*. Third edition. Geneva: WHO; 2004.
- **43** Martin CW, Brown AH, Baird DT. A pilot study of the effect of methotrexate or combined oral contraceptive on bleeding patterns after induction of abortion with mifepristone and a prostaglandin pessary. *Contraception* 1998;58(2):99–103.
- 44 Tang OS, Gao PP, Cheng L, Lee SW, Ho PC. A randomized double-blind placebo-controlled study to assess the effect of oral contraceptive pills on the outcome of medical abortion with mifepristone and misoprostol. *Human Reproduction*. 1999;14(3):722–725.
- **45** Tang OS, Xu J, Cheng L, Lee SW, Ho PC. The effect of contraceptive pills on the measured blood loss in medical termination of pregnancy by mifepristone and misoprostol: a randomized placebo controlled trial. *Human Reproduction*. 2002;17(1):99–102.
- **46** Royal College of Obstetricians and Gynaecologists (RCOG). The Care of Women Requesting Induced Abortion: Evidencebased Clinical Guideline Number 7. London: RCOG Press; 2004.
- **47** Reeves M, Kudva A, Creinin M. Medical abortion outcomes after a second dose of misoprostol for persistent gestational sac. *Contraception.* 2008;78(4):332–335.
- **48** Exelgyn. *Mifepristone Investigators Brochure*. Paris, France: Exelgyn S.A.; 2008.

## Related resources

Castleman L, Winikoff B, Blumenthal P. Providing abortion in low-resource settings. In: Paul M, Lichtenberg S, Borgatta L, Grimes D, Stubblefield P, Creinin M, eds. *Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care.* Wiley-Blackwell; 2009.

Creinin MD and Gemzell Danielsson K. Medical abortion in early pregnancy. In: Paul M, Lichtenberg S, Borgatta L, Grimes D, Stubblefield P, Creinin M, eds. *Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care.* Wiley-Blackwell; 2009.

Gynuity Health Projects and Reproductive Health Technologies Project (RHTP). Frequently asked questions about fatal infection and mifepristone medical abortion: technical version [fact sheet]. New York: Gynuity Health Projects and RHTP; 2006. Available at: www.gynuity.org/ resources/info/faqs-on-fatal-infection-and-medical-abortiontechnical-version/. **Also available in Spanish and Turkish.** 

Hyman AG, Castleman LD. *Woman-centered abortion care: Reference manual*. Chapel Hill, NC: Ipas; 2005. Available at: www.ipas.org/Publications/Woman-centered\_abortion\_ care\_Reference\_manual.aspx. **Also available in French, Portuguese, and Spanish.** 

Hyman AG, McInerny T, Turner K. *Woman-centered abortion care: Trainer's manual.* Chapel Hill, NC: Ipas; 2005. Available at: www.ipas.org/Publications/Woman-centered\_abortion\_ care\_Trainers\_manual.aspx. **Also available in French, Portuguese, and Spanish.** 

Ibis Reproductive Health. *Medication Abortion:* A Training Module for Health Professionals. Cambridge, MA: Ibis Reproductive Health; 2003. Available at: www.ibisreproductivehealth.org/downloads/Medication\_ Abortion\_Training\_Module.ppt. **Also available in Arabic.**  International Consortium for Medical Abortion (ICMA). *The ICMA Information Package on Medical Abortion: Information for Health Care Providers*. Available at: www.medicalabortionconsortium.org/articles/for-healthcare-providers/. **Also available in Arabic, French, Hindi, Portuguese, Romanian, Russian, and Spanish.** 

Ipas. Best practices in medical abortion: starting contraception after first-trimester abortion [fact sheet]. Chapel Hill, NC: Ipas; 2007. Available at: www.ipas.org/ Publications/asset\_upload\_file685\_2890.pdf.

Also available in German, Russian, and Spanish.

McInerny T, Baird TL, Hyman AG, Huber AB. *A Guide to Providing Abortion Care*. Chapel Hill, NC: Ipas; 2001. Available at: www.ipas.org/Publications/asset\_upload\_file207\_2447.pdf. **Also available in Romanian and Russian.** 

Paul M, Stewart FH, Weitz TA, Wilcox N, Tracey JM. *Early Abortion Training Workbook*. San Francisco, CA: University of California, San Francisco Center for Reproductive Health Research & Policy; 2003. Available at: www.teachtraining.org/ Workbook.html.

Philip NM, Shannon C, Winikoff B, eds. *Misoprostol and Teratogenicity: Reviewing the Evidence*. New York: Gynuity Health Projects and Population Council; 2003. Available at: www.gynuityorg/resources/info/misoprostol-and-teratogenicity-reviewing-the-evidence/. **Also available in Spanish.** 

Talluri-Rao S, Baird TL. *Information and Training Guide for Medication-Abortion Counseling*. Chapel Hill, NC: Ipas; 2003. Available at: www.ipas.org/Publications/asset\_upload\_ file24\_2449.pdf. **Also available in Portuguese and Russian**. APPENDIX 3 – DAILY DIARY CARD TEMPLATE

## Home Record for Subject

Study site no..... Subject no.....

## Please mark "x" in the column below for signs & symptoms (S&S) after taken the first drug at hospital

S&S		Bleeding		Lowe	r abdomina	l pain	Naus	sea	Vom	iting	Diarr	hoea	Dizzi	ness	Rash	chills	others
Date	high	moderate	mild	high	moderate	mild	yes	no	yes	no	yes	no	yes	no	yes no	yes no	

## 

**Route of administration** vaginal sublingual

**Remark:** Day 1 = the day when you use misoprostol

S & S		Bleeding		Lowe	r abdomina	l pain	Nausea	a Vomiting		Vomiting Diarrhoea		hoea	Dizziness		Rash	cł	nills	others
Date	high	moderate	mild	high	moderate	mild	yes r	10	yes	no	yes	no	yes	no	yes no	yes	no	
example		Х			Х			X		Х		Х	Х		Х		Х	
Day 1																		
Day 2																		
Day 3																		
Day 4																		
Day 5																		
Day 6																		
Day 7																		
Day 8																		
Day 9																		
Day 10																		
Day 11																		
Day 12																		
Day 13																		
Day 14																		
Day 15																		

Pleases bring this card when visiting the doctor at the hospital

Next follow-up visit: Day......Month .....Year....Year

## List of Changes



Documen	ıt	<ul> <li>➢ Protocol</li> <li>☐ Symptom Diary</li> <li>☐ IB</li> <li>☐ CRF</li> <li>☐ PIS/ICF</li> </ul>
Previous	Version &/or Amendment No.	Version 1.0 Amendment
Newly as	signed Version &/or Amendment No.	Version 1.0 Amendment
Section	Changes	Reason
Page 10	Section title: Background	To specify correct terminology
	Misopristol is a synthetic prostaglandin E1 analogue, initially developed for oral administration and available in a 200-µg dose for the treatment and prophylaxis of Ventricular Ulcus	
	Has been amended to read as	
	Misopristol is a synthetic prostaglandin E1 analogue, initially developed for oral administration and available in a 200- $\mu$ g dose for the treatment and prophylaxis of gastric ulcers (Cytotec)	
Page 15	Section title: Clinical Studies with Medabon	To provide more detailed information.
	Two additional clinical trials of Medabon include an introductory study in Nepal and a prospective uncontrolled study in Vietnam.	
	Has been amended to read as	
	Three additional clinical trials of Medabon include introductory studies in Nepal and Thailand and a prospective uncontrolled study in Vietnam	



## List of Changes ----

----

Page 16	Section title: Clinical Studies with Medabon	To provide more detailed information.
1	The following sentences were added;	
	Pilot introduction of medical abortion with Medabon took place in 2012 in four hospitals in Thailand. A total of 200 women with pregnancies up to 9 weeks were treated and 96% of them had a complete abortion. There were no complications, and 97% of the women were satisfied or highly satisfied with this service model.	
Page 20	Section title: Inclusion Criteria	To precisely define the inclusion criteria
	<ol> <li>On Day 1 of the study (day of mifepristone administration) the duration of pregnancy is not more than 63 days (counted from the first day of last menstrual period) in a normal 28-day cycle.</li> <li>The pregnancy is intrauterine (intrauterine amniotic and appendix of a second results)</li> </ol>	
-	sac seen in ultrasound examination)	· • • • •
	3. A uterine size on pelvic examination compatible with the estimated duration of pregnancy.	
	4. The duration of the pregnancy corresponds to the length of amenorrheal LMP, when verified with ultrasound.	• •
	Has been amended to read as	
	<ol> <li>The duration of pregnancy is not more than 63 days LMP when verified by ultrasound</li> </ol>	
	2. The pregnancy is intrauterine (intrauterine amniotic sac seen in ultrasound examination) (in very early pregnancies the sac may not be seen)	

÷4

## List of Changes



<u> </u>		
Page 21	Section title: Treatment of Subjects	To specify accurate method of administration
	The following sentences were added:	momou of administration
	Misoprostol is to be administered 24 to 48 hours (Day 2	
	or 3) after taking mifepristone. Four tablets of	
	misoprostol (200 µg each) are to be inserted vaginally.	
	Misoprostol may be self-inserted vaginally by either the	
	subject herself or by the doctor or nurse, during a hospital	
	visit or at home.	
	The subject or health worker should use their finger to	
	push the four tablets one at a time into the vagina as far	
	as they are able. Health workers who administer	
	misoprosion vaginarily should follow the instructions of	
	the package insert and wear clean gloves. If women	
	administer misoprostor vaginary memserves enner at	
	home of in the chine, they should be advised to wash	
Page 21	Section title: Sequence of Procedures	To specify more detailed
Ű		information for follow-up
	The following sentences were added;	visit.
	The follow-up visit may take place at a health center or in	
	the hospital (trial site) that treated the women, however,	
	the hospital (trial site) will obtain follow-up report	
	electronically, or telephonically from the health center to	
	facilitate data capture for follow-up visit. Per prescribing	
	information of Medabon, it is recommended that follow-	
	up occur 10 to 14 days after administration of	
	mifepristone. However, this period may be relaxed up to	
	21 days per routine follow-up standards at sites.	



i

## List of Changes -

..

Page 22	Section title: Table 4- Schedule of procedures and	To precisely define the
Ŭ	assessments	activities as per the
	· · · · · · · · · · · · · · · · · · ·	procedures.
	<ul> <li>The following sentences were added;</li> <li>a. Follow-up through 30 days subject to institutional and ethical practice.</li> <li>b. Ultrasound at the follow-up visit if judged necessary from clinical findings.</li> <li>c. Assessment of complete abortion, incomplete abortion, missed abortion, continued pregnancy, or undetermined, on the basis of the subject's history and the clinical findings or pelvic ultrasound examination.</li> <li>d. The follow-up visit may take place at a health center or in the hospital (trial site) that treated the women, however, the hospital (trial site) will obtain follow-up report electronically, or telephonically from the health center to facilitate data capture for follow-up visit. Per prescribing information of Medabon, it is recommended that follow-up occur 10 to 14 days after administration of mifepristone. However, this period may be relaxed up to 21 days per routine follow-up standards at sites.</li> <li>e. If misoprostol is inserted vaginally by either the subject herself or by a doctor or nurse at a location different from the trial site, an electronic or telephonic interview of the subject will be conducted</li> </ul>	
Page 24	Section title: Study Assessments During the	To correct the
	Observational Period	typographical errors with
		respect to visit days.
	1. Day $\overline{3}$	· -
	2. Follow-up Visit (Day 11 through Day 15)	
	Has been amended to read as	
	<ol> <li>Day 2-3</li> <li>Follow-up Visit (Day 10 through Day 21)</li> </ol>	

¥

## List of Changes



Page 24	Section title: Follow-up Through day 30	To define the follow-up
		visit
	The following sentences were added;	
	This is optional as none of the three centres in the study	
	follow up to 30 days. However, wherever possible.	
	medical records may be electronically accessed to note	
	whether any additional treatments were needed up to 30	
	deve after mifenristone	
	uays and inneprisione.	
D 22	Section title Ethics Committee	To provide precise
Page 35	Section title: Ethics Committee	information
		mormation
	The investigator will submit status reports to the EC at	
	least annually (when applicable).	
	Has been amended to read as	
	The investigator will submit status reports to the EC as per	
1	local requirements	
Entire	In the Entire Protocol	To precisely define the
Protocol		term
	The word "Patients" has been <i>replaced</i> with word	
	"Subjects"	
Annend	Section title: Appendix	To complete the protocol
iv	Presson and when and	1 1
	The following were added:	
	The johowing were unucu,	
	Annendix 2 Doily Doiry Card Template	
	Appendix 5 – Dany Dany Calu Template	

Prepared By: Vidhi Kuvadia Vidhi <sub>23</sub> Aug - 2013 Name, Sign & Date Checked By: Shravanti Bhowmik

-3 AUG 2013.

Name, Sign & Date

Page 5 of 5



Medical and Service Delivery Guidelines

## Medabon®: Medical and Service Delivery Guidelines

## Contents

## **SECTION 1**

Background information on Medabon®

## SECTION 2

Screening for Medabon®

## SECTION 3

Prescribing and administering Medabon®

## SECTION 4 Following up

#### REFERENCES

#### **RELATED RESOURCES**

These guidelines represent a consensus view of three agencies for the Medabon<sup>®</sup> product that may differ from their own general medical abortion protocols.

This document can be found online at www.medabon.info. To request additional copies, please contact Concept Foundation at medabon@conceptfoundation.org. Medabon<sup>®</sup> is a combination therapy for medical abortion in pregnancies through nine weeks, or up to and including 63 days since a woman's last menstrual period (LMP). Medical abortion refers to the process of ending a pregnancy by taking medication, rather than through surgical intervention.<sup>\*</sup> It may also be referred to as medication abortion, the abortion pill, non-aspiration abortion, or non-surgical abortion. The term "medical abortion" does not mean that a physician needs to be involved or that the procedure is performed out of medical necessity.

Medical abortion has been used by millions of women throughout the world. In 2006, the World Health Organization (WHO) released updated recommendations on medical abortion based on available evidence.<sup>1</sup> According to these recommendations, medical abortion through nine weeks' gestation is safe and effective. The most effective and safest medical abortion regimen requires the use of two drugs, mifepristone and misoprostol. Medabon<sup>®</sup> packages contain mifepristone and misoprostol together.

This document on Medabon<sup>®</sup> has four sections that roughly correspond to the medical abortion process from a health worker's perspective: background information, screening, administration, and followup. The protocol on page 9 provides an overview of the medical abortion process using Medabon<sup>®</sup>. This document was developed for an audience with a moderate amount of medical expertise. The level of technical detail and language may be adapted for the health providers who will be implementing services in a specific setting.

\* The term "surgical abortion" is often used to refer to procedures such as vacuum aspiration (electric or manual) and sharp curettage, also known as dilatation and curettage (D&C).

## Background information on Medabon®

Mifepristone and misoprostol are licensed separately in many countries. Medabon<sup>®</sup> offers the benefit of the drugs being licensed and packaged together in one medical abortion product.



Mifepristone acts by blocking progesterone receptors, leading to changes in the endometrial lining so that it ceases to support pregnancy, softening and dilation of the cervix, and increased uterine sensitivity to prostaglandins (such as misoprostol).<sup>2</sup>

Misoprostol is the preferred prostaglandin analog for use with mifepristone because of its efficacy, safety, low cost, and wide availability.<sup>3</sup> Misoprostol softens the cervix and increases uterine contractility, and the contractions expel the pregnancy.

## **Dosing and regimen**

The Medabon® regimen consists of one 200-mg tablet of mifepristone given orally, followed one to two days (24 to 48 hours) later by four 200-µg tablets of misoprostol. This is the regimen recommended by WHO as a safe and effective method for medical abortion.<sup>1</sup>

## Misoprostol administration

Women have options in terms of when and how they can take misoprostol.\* Providers should discuss these options with each woman taking Medabon<sup>®</sup> so that she can choose the regimen most optimal to her needs and preferences.

## **MISOPROSTOL** administration

(Day 1 is mifepristone day)

Route	Timing
Vaginal (800 µg)	Day 2 or 3
Sublingual (800 µg)	(24–48 nours after mifepristone)

Medabon® is registered for vaginal and sublingual use of misoprostol. See page 8 for complete instructions regarding administration of misoprostol, including through vaginal and sublingual routes. There is additional evidence that buccal use of misoprostol (i.e., inserting pills between the cheek and the gum) is also effective and is widely used in some countries,<sup>8–10</sup> but Medabon® is not currently labeled for this route.

Medical abortion with Medabon<sup>®</sup> generally requires three steps:

- 1 Administration of mifepristone.
- 2 Administration of misoprostol one to two days later.
- **3** A follow-up assessment one to two weeks (generally 10–14 days) after mifepristone administration to confirm completion of abortion.

\* The initial registrations and labeling for Medabon<sup>®</sup> recommended that misoprostol be used vaginally 36–48 hours after mifepristone. Since then, Concept Foundation has gained access to data showing that misoprostol can be administered safely and effectively by the sublingual route,<sup>4,5</sup> and misoprostol can be administered by both the vaginal and sublingual routes 24–48 hours post-mifepristone.<sup>6,7</sup> These changes are being made to regulatory submissions and eventually to packaging materials. Despite this original labeling, providers may wish to comply with the new evidence-based regimens stated in these guidelines.

## Effectiveness

An effective medical abortion is generally defined as a pregnancy terminated without need for another uterine evacuation method, such as vacuum aspiration or curettage. The Medabon® regimen has been shown to achieve complete abortion in about 98 percent of cases, and less than 1 percent of women using this regimen experience ongoing, viable pregnancies.<sup>5,11</sup>

The rate of complete abortion for the Medabon<sup>®</sup> regimen can vary by provider. As provider experience increases, they are likely to be more comfortable with the method and less likely to perform unnecessary interventions. Following the regimen outlined in these guidelines will help ensure the highest rates of success. For example, adhering to the suggested interval between administration of misoprostol and a follow-up visit will help ensure that a woman's abortion has had time to complete and will make unnecessary intervention less common. Of course, women should seek follow-up care sooner if they have problems or concerns.

## **Expected effects**

Vaginal bleeding and cramping are normal and expected. The medical abortion process may feel like an intense, crampy, and long menstrual period, or similar to a spontaneous miscarriage.

Vaginal bleeding, often accompanied by the passage of clots, is usually heavier than a menstrual period. Bleeding sometimes begins after taking mifepristone, but most often starts one to three hours after misoprostol is taken. The amount and duration of bleeding varies: bleeding is generally heaviest for a few hours during the actual abortion and has the general pattern of diminishing over time, often lasting up to two to three weeks. Cramping is typically strongest in the hours after misoprostol is taken, then eases off after the pregnancy is expelled.<sup>12</sup>

After the pregnancy passes, which the woman may not be able to differentiate from other blood and/or clots, she will likely experience a persistent decrease of bleeding and cramps until the bleeding ends.

## Side effects

Uterine contractions can be painful, and some women will experience side effects—including nausea, vomiting, diarrhea, headache, chills, shivering, and transient fever lasting less than a day. There are no long-term health effects of Medabon®, nor will the medication impact any future pregnancies.<sup>13</sup>

### Medabon<sup>®</sup> key facts

- Medabon<sup>®</sup> consists of two medicines: mifepristone and misoprostol.
- The Medabon<sup>®</sup> regimen is in line with current (as of June 2009) WHO recommendations for medical abortion<sup>1</sup>: one 200-mg tablet of mifepristone given orally, followed 24–48 hours later by four 200-µg tablets of misoprostol. The four misoprostol tablets can be administered vaginally or sublingually.
- Medabon® is registered for use in pregnancies through nine weeks (63 days) since a woman's LMP.
- Medical abortion with mifepristone and misoprostol has been shown to be 98 percent effective when used through nine weeks (63 days) since LMP.<sup>5</sup>

# **2** Screening for Medabon<sup>®</sup>

## Contraindications

There are very few situations that absolutely exclude a woman from taking Medabon<sup>®</sup>.

## Women cannot take Medabon® if they:

- Are allergic to any of the drugs involved (mifepristone, misoprostol, or another prostaglandin).
- Have inherited porphyria, a rare blood disorder.<sup>14</sup>
- Have a hemorrhagic disorder or are on concurrent anticoagulant therapy, unless transfusion services are available (there is very limited evidence describing provision of medical abortion in such cases).
- Have a known or suspected ectopic pregnancy.

## **Precautions**

## Women with these conditions should be treated with caution specific to their situation:

- Currently taking long-term systemic corticosteroid therapy for asthma or other conditions.<sup>15,16</sup> By contrast, the medicines in asthma inhalers are not systemically absorbed and women taking these medicines may use Medabon<sup>®</sup>.
- Chronic adrenal failure. It is possible that women with chronic adrenal failure may acutely develop dehydration, low blood pressure, or shock after taking mifepristone. Women with chronic adrenal failure should take an increased dose of glucocorticoids when using mifepristone and should be carefully monitored for signs and symptoms of shock.<sup>15,16</sup>

**Note:** Women with multiple gestation<sup>17</sup> and obese women<sup>18</sup> may be given Medabon<sup>®</sup> in the same doses as other women. Additionally, women who have used Medabon<sup>®</sup> in the past may use it again with no decrease in efficacy.

## **Special considerations**

There is little evidence on the use of medical abortion in women with the following conditions: severe anemia (hemoglobin level < 9 g/dL), clinical illness or unstable health problems, or sepsis. Whether to administer medical abortion to women with these conditions will depend on the available options for safe abortion care, referrals, and clinical judgment.

The following women can take Medabon<sup>®</sup>, but may require additional information or clinical care:

- Women who are breastfeeding. Misoprostol enters breast milk soon after administration, and it is likely that mifepristone does as well. There is no evidence to suggest that either medication is harmful to infants. Women who are concerned about the effects of misoprostol on infants can take the medication immediately after nursing.<sup>19</sup>
- Women with an intrauterine device (IUD). Women with an IUD can be treated with Medabon<sup>®</sup> as long as the IUD is removed beforehand. See page 11 for information on reinitiating contraception after taking Medabon<sup>®</sup>.
- Women with sexually transmitted infections (STIs). Women with a confirmed STI should be treated concurrently with the initiation of medical abortion. Women with a suspected STI should be evaluated or referred and treated as appropriate for the health care setting; however, treatment of suspected STIs should not delay the abortion.

Given that Medabon<sup>®</sup> is only licensed for pregnancies through nine weeks, the likelihood of Rh-sensitization is very low. There is currently not enough evidence to recommend for or against Rh screening through nine weeks since LMP.<sup>20</sup> Depending on the prevalence of RhD-negative blood in the population and the ability to offer Rh-immune globulin, the country standard should be followed.

## Confirming pregnancy and timing

Medabon<sup>®</sup> is licensed for women with pregnancies through nine weeks: in other words, a woman can take Medabon<sup>®</sup> through 63 days after the first day of her LMP.

Duration of pregnancy can generally be confirmed by taking the woman's history and with a physical examination. If signs of pregnancy are not clearly present, a blood or urine test confirming pregnancy may be required. Ultrasound is not necessary and should not be a prerequisite for abortion in settings where it is unavailable or makes the procedure overly expensive.<sup>1,21</sup> Where ultrasound is available, it may help to determine the length of pregnancy in cases of a discrepancy in dating, or to confirm an intrauterine pregnancy.

## Choosing medical abortion or vacuum aspiration

Both medical abortion and vacuum aspiration have been found to be acceptable methods to women.<sup>22,23,24</sup> Women are more likely to find a method acceptable if they have chosen it themselves.<sup>25,26</sup>

Women choose medical abortion or vacuum aspiration for a variety of reasons that reflect a woman's specific circumstances and cultural context. Factors women consider in choosing between available methods include the length of gestation, the duration of the abortion process, where the abortion will occur, and what they are likely to experience.<sup>23</sup>

Both medical abortion and vacuum aspiration are safe and effective methods with low complication rates.<sup>11,27</sup> There are, therefore, very few situations where a clear medical preference for either method exists.

## Undiagnosed ectopic pregnancy

An ectopic pregnancy is a pregnancy located outside the uterine cavity. Medabon® does not treat ectopic pregnancy, a preexisting condition rather than a complication of the abortion procedure. Therefore, ectopic pregnancy may be diagnosed when a woman seeking a medical abortion undergoes clinical assessment before the procedure. However, ectopic pregnancy can go undetected during clinical assessment and even remain undetected after a medical abortion is performed. A woman may still experience bleeding and cramping after taking Medabon<sup>®</sup>, even if she has an ectopic pregnancy, and a provider is unlikely to examine the expelled tissue to confirm termination of pregnancy. Therefore, diagnosis and treatment of ectopic pregnancy may take place in the course of follow-up.

Typical symptoms of ectopic pregnancy are abdominal or pelvic pain—often one-sided and vaginal bleeding. Pain and bleeding may be persistent or erratic and variable and, in some cases, absent.<sup>28</sup> High-risk factors for ectopic pregnancy are tubal surgery, tubal sterilization, previous ectopic pregnancy, in utero exposure to diethylstilbestrol, use of intrauterine device (IUD)\*, and documented tubal disease.<sup>30</sup>

Ectopic pregnancy can sometimes be confirmed with an ultrasound, but often an ultrasound can only confirm the absence of an intrauterine pregnancy. With serial  $\beta$ -hCG measurements *and* ultrasound showing an empty uterine cavity in an asymptomatic patient, ectopic pregnancy can be strongly suspected. It is rare to actually see the ectopic pregnancy on ultrasound, unless a very good unit, a transvaginal probe, or a highly skilled sonographer is available and the patient's pelvic anatomy and location of the ectopic pregnancy permit visualization. If ultrasound is not available and ectopic pregnancy is suspected, or if the woman is symptomatic for ectopic pregnancy, she should be referred to an appropriate gynecology service for urgent treatment.

\* Women with an IUD in place and those who have had tubal ligation are more likely to have an ectopic than intrauterine pregnancy if conception does occur, but their baseline risk of pregnancy is far lower than that of women not using contraception.<sup>29</sup>

Possible reasons to recommend **medical abortion**:

- Severe obesity. A surgical procedure may be more technically challenging.<sup>1</sup>
- Uterine malformations, a fibroid uterus, or previous cervical stenosis.
- A wish to avoid an invasive procedure.

Possible reasons to recommend **surgical abortion** (usually vacuum aspiration):

- Contraindications to medical abortion.
- Time or geographical constraints preclude follow-up to confirm that medical abortion is complete.
- A woman has made the free and informed choice that she would like to be sterilized or have an IUD inserted, and the procedures can be carried out at the same time.
- Suspected ectopic pregnancy (so tissue can be examined to verify complete abortion).

Each woman who chooses medical abortion should be clearly informed:

- What will be done at each visit and what she will experience or do at home.
- What the medical abortion may feel like.
- What the common side effects are.
- How long the process may take.
- What the potential risks and complications are.
- What pain medications are available and how to use them.
- That she must plan to complete the abortion process once she starts it.
- When she will be able to resume her normal activities, including sexual intercourse.
- When she needs to seek medical attention.
- What contraceptive methods are available and how to get/start them.



## Prescribing and administering Medabon<sup>®</sup>

## Scheduling medical abortion with Medabon®

The full medical abortion process should be taken into consideration when health providers and women schedule clinic visits. For most women, expulsion will happen within four to six hours of taking misoprostol.<sup>31</sup> Bleeding and cramping will likely be heaviest at this time. If misoprostol is administered in a clinic setting, it is advisable that a woman stays in the clinic until she feels comfortable and able to return home. Women should be informed of this in advance so that they can plan for misoprostol administration around travel time, work and family needs, and the ability to have someone there with her if she chooses.

Women should have access to emergency care during the medical abortion process. Providers and women should make a plan for where to seek emergency care in the rare event of a serious complication.

## Medabon® administration

- **Step 1.** Woman swallows one mifepristone pill. If a woman vomits within 30 minutes of taking mifepristone, she will need to take another mifepristone pill.
- **Step 2.** Four 200-μg misoprostol tablets are administered one or two days (24–48 hours) later (see box "Misoprostol administration," page 3).

*Vaginal administration:* The woman or health worker should use their finger to push the four tablets one at a time into the vagina as far as they are able.

Health workers who administer misoprostol vaginally should follow the instructions on the package insert and wear clean gloves. If women administer misoprostol vaginally themselves, either at home or in the clinic, they should be advised to wash their hands first. Sublingual administration: Women should place two tablets of misoprostol under their tongue and wait for them to dissolve. As soon as they have dissolved, two more tablets can be taken in the same way. If the first two tablets have not dissolved after 20 minutes, women can swallow any remaining fragments and take the final two tablets.

Some women may prefer to take all four tablets at once. In that case, women should place all four tablets under the tongue and wait for them to dissolve. If they have not dissolved after 20 minutes, women can swallow any remaining fragments.

Swallowing the tablets whole (oral administration) is less effective than placing them under the tongue until they dissolve or for 20 minutes.<sup>5</sup>

More information on **Step 3**, the follow-up visit, is provided on page 12.

## **Resuming normal activities**

Women should have clear expectations regarding when they will or can resume normal activities. For example:

- Showering and bathing are fine at any time in the medical abortion process. Vaginal douching is not recommended.<sup>32</sup>
- Women may ask when they are able to resume sexual activity. There is no evidence base to suggest ideal timing, but women should be encouraged to wait until they feel comfortable and ready (see below).
- Women can ovulate, and therefore get pregnant, before menstruation returns to normal. Women who want to prevent pregnancy should use a contraceptive method during sexual relations after taking Medabon<sup>®</sup>.
   Women have been found to ovulate as early as ten days following abortion. See page 11 for more information about contraceptive options.
- The return of menses following medical abortion will generally occur after about five weeks.<sup>33</sup>

## Medabon® Clinic Visits and Protocol

#### **STEP 1** Initial clinic visit and mifepristone administration

- Confirm pregnancy and length of pregnancy.
- Counsel woman on pregnancy/abortion options.
- · Complete physical exam and medical history.
- Screen for contraindications and risk factors.
- Rule out ectopic pregnancy.

## For women who choose Medabon<sup>®</sup> and will take misoprostol **in the clinic:**

- Counsel woman on what to expect.
- Create schedule of Medabon<sup>®</sup> visits.
- Create plan for emergency follow-up care.
- Provide suggestions for dealing with side effects.
- Woman takes mifepristone orally.

For women who choose Medabon<sup>®</sup> and will take misoprostol **at home:** 

- Counsel woman on how to administer misoprostol vaginally or sublingually, using visual aids as appropriate.
- Review signs of serious complications and confirm woman has printed materials.
- Create plan for emergency follow-up care.
- Provide suggestions for dealing with side effects and make pain medication available.
- Schedule follow-up visit.
- Provide misoprostol tablets to take home.
- Woman takes mifepristone orally.

#### **STEP 2** Misoprostol administration (24–48 hours later)

### In the clinic:

- Administer misoprostol vaginally or sublingually.
- Make pain medication available.
- Review signs of serious complications and confirm woman has printed materials.
- Review plans for follow-up visit.
- Review side effects and management.

#### At home:

• Woman administers misoprostol vaginally or sublingually.

## Contraception

Discuss contraceptive options early in the process.

The woman's choice of method will determine when contraception is provided.

#### **STEP 3** Follow-up visit (10–14 days after mifepristone administration)

- Confirm that abortion is successful (most women will be in this category).
- If the woman is experiencing problematic bleeding (see page 12 for more detail), treatment options include:
  - Waiting longer for bleeding to stop.
  - An additional dose of misoprostol.
  - Uterine evacuation.
- In the case of continuing pregnancy, uterine evacuation is recommended.

## Managing effects of the abortion

### Bleeding

Bleeding can be managed similarly to a very heavy menstrual period or a spontaneous miscarriage (e.g., with sanitary pads or cotton wool). It will be heaviest after taking misoprostol—often during expulsion of the products of conception—and light bleeding may last two weeks or longer. It is not uncommon for bleeding to stop and then start again. Some women, up to 20 percent in one study, may continue to have bleeding or spotting 35–42 days after the initiation of a medical abortion.<sup>34</sup> If bleeding is heavy, prolonged, or causes anemia (or symptoms of anemia, such as dizziness, faintness, or significant loss of energy), then vacuum aspiration, fluid replacement, or transfusion might be required. The risk of bleeding requiring intervention (transfusion and/or aspiration) ranges from 0.02 to 1.8 percent.35-37

### Cramping and pain

Women are most likely to feel pain in the first few hours after administration of misoprostol.<sup>1</sup> Women should receive medicines (or where they are unavailable, prescriptions or recommendations for medicines) to manage pain and have the pain medicine available when taking the misoprostol. Nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen (400–800 mg) have been shown to be more effective than paracetamol (500–1,000 mg)<sup>38</sup> and can be taken at the same time as misoprostol, but not before. If possible, women should have access to or at least a prescription for a narcotic pain medicine in the event they need it; codeine 30–40 mg may be added to either NSAIDs or paracetamol. Women should be advised of other comfort measures, such as use of hot water bottles.

## Seeking care for possible complications

When educating women about the use of Medabon<sup>®</sup>, it is important to stress that serious complications are rare, but that they should be on the look-out for the following signs and symptoms, and seek help (ideally from their original provider) if they experience:

- Persistent, heavy bleeding to the point where they feel sick or weak, or if they soak more than two pads per hour for more than two consecutive hours.
- Fever of 38°C/100.4°F or higher continuing for more than the day following misoprostol use.
- Persistent vomiting or diarrhea for more than the day on which misoprostol was administered.
- Very severe, continuous, or increasing abdominal pain that is unrelieved by medication, rest, a hot water bottle, or a heating pad.

Little to no bleeding 24–48 hours following misoprostol is not an emergency, but is cause for seeking follow-up care as it may be a sign of continued pregnancy.

Infection after medical abortion procedures is rare. Women should, however, be informed of the symptoms of infection and encouraged to seek follow-up care should symptoms of infection occur. The severity of the infection should determine what treatment is provided; oral antibiotics are used for most treatment of infection or presumed infection.<sup>39</sup>

Women should always be given printed information on signs of complications to take home (see the sample patient brochure in these materials). As noted previously, providers and women should discuss a plan for emergency care prior to the medical abortion process. Ideally, women should seek care for complications from their original providers. If the original provider is not available, accessible, or cannot provide the necessary follow-up, providers should work with women to identify an alternative in advance. Women should be encouraged to take their informational materials with them if they seek emergency care elsewhere, in case the facility is unfamiliar with medical abortion and associated complications.
Most back-up care is similar to that needed by women having a spontaneous abortion, and many communities have a health care facility already in place to provide such care. In rare cases, serious complications do occur that require emergency follow-up (see the "Medical Guidelines for Providers of Emergency Care" included in this packet).

#### **Contraceptive counseling and services**

Women taking Medabon<sup>®</sup> should be offered contraception. Women can become pregnant within ten days of the abortion if they are not using an effective method of contraception.<sup>40</sup> Evidence supports the use of any modern contraceptive method after an uncomplicated abortion.<sup>41,42</sup>

Women can begin taking hormonal methods, whether combined (estrogen and progestin) or progestin-only, on the same day as misoprostol administration, when expulsion of the products of conception generally occurs.<sup>43</sup> These methods include oral contraceptives,<sup>44–46</sup> injectable methods, implants, and the contraceptive patch. For women taking the misoprostol at home, they can be given any patient-initiated hormonal methods and told to start them on the day they take misoprostol. They may see a provider for injectable contraception or implants. The vaginal contraceptive ring can be started when bleeding slows down after expulsion of the pregnancy. Condoms, spermicides, the cervical cap, and the diaphragm can be used as soon as women start having sex again.<sup>1</sup> If a woman would like to have an IUD inserted or undergo sterilization, these procedures should be performed after an assessment confirms that the woman is no longer pregnant and the products of conception have been expelled.

Natural family planning or fertility-awareness methods cannot be initiated until a woman's regular cycles have resumed, and she may need to use a barrier method like a condom or a diaphragm—in the meantime.

# 4 Following up

A follow-up visit is desirable approximately two weeks (10–14 days) after taking Medabon<sup>®</sup>. During this visit, the clinician confirms that the woman is no longer pregnant and that bleeding patterns are within the expected range, ensures contraception is provided if desired, and answers her questions. Confirmation that the pregnancy has been terminated is possible by pelvic examination, bleeding and symptom history, or by ultrasound, if necessary.

The following scenarios represent the most likely situations encountered at the follow-up visit:

#### Successful medical abortion

The woman reports she no longer feels pregnant, has taken the medications as instructed, and had bleeding and cramping consistent with a successful medical abortion. This is the most common outcome.

## **Problematic bleeding**

Problematic bleeding encompasses a range of bleeding patterns that may be tiresome or problematic for the woman, or, in rare cases, are true emergencies. In the case of problematic bleeding, the pregnancy is not growing, but the woman's bleeding pattern is not gradually diminishing. The pelvic exam is consistent with a small or non-pregnant uterus. Treatment options, unless indicated otherwise below, are: 1) waiting longer for bleeding to stop; 2) an additional dose of misoprostol, which may help the uterus contract and expel residual tissue or a persistent empty sac; or 3) uterine evacuation.

Various patterns of problematic bleeding requiring specific interventions are:

• Persistently heavy bleeding. The woman may have been bleeding continuously—like during a heavy menstrual period—since she took misoprostol. If the woman feels weak from bleeding, a uterine aspiration is recommended. If she is clinically stable and feels well, a repeat dose of misoprostol may be offered as long as the woman is willing and able to return two days to one week later, depending on the duration and amount of problematic bleeding, to assess whether bleeding is diminishing.<sup>45</sup> Although providing a second dose of misoprostol is a practice used by some providers to increase uterine contractility and expel residual tissue, its use has been studied for expulsion of a persistent sac or unexpelled embryo<sup>47</sup>; providing a repeat dose of misoprostol has not been studied for alleviation of problematic bleeding.

- Erratic bleeding. Some women have days of very little bleeding, no bleeding, or spotting, and erratically experience very heavy, gushing bleeding. If a woman is symptomatic for anemia, perform uterine aspiration.
- Hemorrhage. Hemorrhage causing hemodynamic instability is an emergency and is treated with an immediate uterine evacuation to empty the uterus. If the hemorrhage has been very serious, blood or fluid transfusion should be considered. If transfusion services are not available, the woman should be transported to the nearest facility providing these services.

### **Continued pregnancy**

The woman reports continued pregnancy symptoms and the uterus is larger than on previous exam. Uterine evacuation is recommended at this time.

### Possible birth defects if pregnancy continues

Evidence on birth defects associated with mifepristone or misoprostol are inconclusive. From an estimated two million procedures performed between 1987 and 2008 in countries where Exelgyn Laboratories holds marketing authorization for a mifepristone product—Mifegyne®—a total of 26 malformations have been reported in cases where the combined treatment failed or the woman changed her mind about the procedure after taking the mifepristone.<sup>48</sup> Six cases of malformation have been reported after use of mifepristone alone, and twenty other cases have been reported after use of mifepristone and a prostaglandin. According to these authors, none of the events have been conclusively related to the treatment.

Women who choose to carry a pregnancy to term should be counseled on the possibility of birth defects and encouraged to seek active follow-up care throughout pregnancy.

#### References

- 1 World Health Organization (WHO). Frequently Asked Questions about Medical Abortion: Conclusions of an International Consensus Conference on Medical Abortion in Early First Trimester, Bellagio, Italy. Geneva: WHO; 2006. Available at: www.who.int/ reproductive-health/publications/medical\_abortion/.
- 2 Creinin M. Medical abortion regimens: historical context and overview. *American Journal of Obstetrics & Gynecology*. 2000;(2Suppl):S3–S9.
- 3 Foster A. Medication Abortion: A Guide for Health Professionals. Cambridge: Ibis Reproductive Health; 2005. Available at: www.ibisreproductivehealth.org/downloads/Medication\_ abortion\_A\_guide\_for\_health\_professionals\_English.pdf.
- 4 Tang OS, Chan C, Ng E, Lee S, Ho P. 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. *Human Reproduction*. 2003;18(11):2315–2318.
- Raghavan S, Comendant R, Digol I, et al. Two-pill regimens of misoprostol after mifepristone medical abortion through 63 days' gestational age: a randomized controlled trial of sublingual and oral misoprostol. *Contraception*. 2009; 79(2):84–90.
- 6 Hamoda H, Ashok PW, Dow J, Flett GM, Templeton A. A pilot study of mifepristone in combination with sublingual or vaginal misoprostol for medical termination of pregnancy up to 63 days gestation. *Contraception*. 2003;68(5):335–338.
- von Hertzen H, Piaggio G, Wojdyla D, et al. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomized factorial controlled equivalence trial. *British Journal of Obstetrics and Gynaecology.* 2009;116(3):381–389.
- 8 Winikoff B, Dzuba IG, Creinin MD, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstetrics & Gynecology*. 2008;112(6):1303–1310.
- Fjerstad M, Sivin I, Lichtenberg ES, Trussel J, Cleland K, Cullins V. Effectiveness of medical abortion with mifepristone and buccal misoprostol through 59 gestational days. *Contraception*. In press.
- 10 Middleton T, Schaff E, Fielding S, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception*. 2005;72(5):328–332.

- 11 Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. Factors affecting the outcome of early medical abortion: a review of 4132 consecutive cases. *British Journal of Obstetrics and Gynaecology*. 2002;109(11):1281–1289.
- 12 Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. *New England Journal of Medicine*. 1998;338(18):1241–1247.
- 13 Virk J, Zhang J, Olsen J. Medical abortion and the risk of subsequent adverse pregnancy outcomes. *New England Journal of Medicine*. 2007;357:648–653.
- 14 Cable EE, Pepe JA, Donohue SE, Lambrecht RW, Bonkovsky HL. Effects of mifepristone (RU-486) on heme metabolism and cytochromes P-450 in cultured chick embryo liver cells, possible implications for acute porphyria. *European Journal of Biochemistry*. 1994;225(2):651–657.
- Sitruk-Ware R. Mifepristone and misoprostol sequential regimen side effects, complications and safety. *Contraception*. 2006;74(1):48–55.
- 16 Davey A. Mifepristone and prostaglandin for termination of pregnancy: contraindications for use, reasons and rationale. *Contraception*. 2006;74(1):16–20.
- 17 Hayes JL, Achilles S, Reeves MF, Creinin MD. Outcomes of medical abortion through 63 days in women with twin gestations. *Contraception*. 2008;78(2):168–169.
- Strafford M, Mottl-Santiago J, Savla A, Soodoo N, Borgatta L. Relationship of obesity to outcome of medical abortion. *American Journal of Obstetrics & Gynecology*. 2009;200(5): e34–36.
- 19 Vogel D, Burkhardt T, Rentsch K, et al. Misoprostol versus methylergometrine: pharmacokinetics in human milk. *American Journal of Obstetrics & Gynecology*. 2004;191(6): 2168–2173.
- Fiala C, Fux M, Gemzell-Danielsson K. Rh-prophylaxis in early abortion. *Acta Obstetricia et Gynecologica Scandinavica*. 2003;82(10):892–903.
- 21 World Health Organization (WHO). *Safe Abortion: Technical and Policy Guidance for Health Systems*. Geneva: WHO; 2003. Available at: www.who.int/reproductive-health/publications/ safe\_abortion/.

- 22 Creinin, MD. Randomized comparison of efficacy, acceptability and cost of medical versus surgical abortion. *Contraception*. 2000;62(3):117–124.
- 23 Winikoff B, Irving S, Kurus J, et al. Safety, efficacy, and acceptability of medical abortion in China, Cuba, and India: a comparative trial of mifepristone-misoprostol versus surgical abortion. *American Journal of Obstetrics & Gynecology*. 1997;176(2):431–437.
- 24 Tang OS, Miao BY, Lee SW, Ho PC. Pilot study on the use of repeated doses of sublingual misoprostol in termination of pregnancy up to 12 weeks gestation: efficacy and acceptability. *Human Reproduction*. 2002;17(3):654–658.
- 25 Henshaw RC, Naji SA, Russell IT, Templeton AA. Comparison of medical abortion with surgical vacuum aspiration: women's preferences and acceptability of treatment. *British Medical Journal*. 1993;307(6906):714–717.
- 26 Slade P, Heke S, Fletcher J, Stewart P. A comparison of medical and surgical termination of pregnancy: choice, emotional impact and satisfaction with care. *British Journal of Obstetrics and Gynaecology*. 1998;105(12):1288–1295.
- 27 Hakim-Elahi E, Towell HM, Burnhill MS. Complications of first trimester abortion: a report of 170,000 cases. *Obstetrics & Gynecology*. 1990;76(1):129–135.
- 28 Seeber B, Barnhart K. Suspected ectopic pregnancy. Obstetrics & Gynecology. 2006;107:399–413.
- 29 Rossing M, Daling J, Voigt L, Stergachis A, Weiss N. Current use of an intrauterine device and risk of tubal pregnancy. *Epidemiology*. 1993;4(3):252–258.
- 30 Pisarka M, Carson S, Buster J. Ectopic pregnancy. *The Lancet*. 1998;351:1115.
- El-Refaey H, Templeton A. Early induction of abortion by a combination of oral mifepristone and misoprostol administered by the vaginal route. *Contraception*. 1994;49(2):111–114.
- **32** Tsai CS, Shepherd BE, Vermund SH. Does douching increase risk for sexually transmitted infections? A prospective study in high-risk adolescents. *American Journal of Obstetrics & Gynecology*. 2009;200(1):38.e1–8.
- **33** World Health Organization Task Force on Post-ovulatory Methods for Fertility Regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomized trial. *British Journal of Obstetrics and Gynaecology*. 2000;107(4):524–530.
- 34 Davis A, Westhoff C, De Nonno L. Bleeding patterns after early abortion with mifepristone and misoprostol or manual vacuum aspiration. *Journal of the American Medical Women's Association*. 2000;55(3Suppl):141–144.

- 35 Ashok PW, Penney GC, Flett GM, Templeton A. An effective regimen for early medical abortion: a report of 2000 consecutive cases. *Human Reproduction*. 1998;13(10): 2962–2965.
- 36 Hausknecht R. Mifepristone and misoprostol for early medical abortion: 18 months experience in the United States. *Contraception*. 2003;67(6):463–465.
- 37 Schaff E, Stadalius L, Eisinger S, Franks P. Vaginal misoprostol administered at home after mifepristone (RU486) for abortion. *Journal of Family Practice*. 1997;44(4):353–361.
- 38 Livshits A, Machtinger R, David LB, Spira M, Moshe-Zahav A, Seidman DS. Ibuprofen and paracetamol for pain relief during medical abortion: a double-blind randomized controlled study. *Fertility and Sterility*. 2009;91(5):1877–1880.
- 39 Shannon C, Brothers LP, Philip NM, Winikoff B. Infection after medical abortion: a review of the literature. *Contraception*. 2004;70(3):183–190.
- 40 Boyd EF Jr, Holmstrom EG. Ovulation following therapeutic abortion. *American Journal of Obstetrics & Gynecology*. 1972;113(4):469–473.
- **41** Mittal S. Contraception after medical abortion. *Contraception*. 2006;74(1):56–60.
- 42 World Health Organization (WHO). *Medical eligibility criteria for contraceptive use*. Third edition. Geneva: WHO; 2004.
- **43** Martin CW, Brown AH, Baird DT. A pilot study of the effect of methotrexate or combined oral contraceptive on bleeding patterns after induction of abortion with mifepristone and a prostaglandin pessary. *Contraception* 1998;58(2):99–103.
- 44 Tang OS, Gao PP, Cheng L, Lee SW, Ho PC. A randomized double-blind placebo-controlled study to assess the effect of oral contraceptive pills on the outcome of medical abortion with mifepristone and misoprostol. *Human Reproduction*. 1999;14(3):722–725.
- Tang OS, Xu J, Cheng L, Lee SW, Ho PC. The effect of contraceptive pills on the measured blood loss in medical termination of pregnancy by mifepristone and misoprostol: a randomized placebo controlled trial. *Human Reproduction*. 2002;17(1):99–102.
- **46** Royal College of Obstetricians and Gynaecologists (RCOG). The Care of Women Requesting Induced Abortion: Evidencebased Clinical Guideline Number 7. London: RCOG Press; 2004.
- **47** Reeves M, Kudva A, Creinin M. Medical abortion outcomes after a second dose of misoprostol for persistent gestational sac. *Contraception.* 2008;78(4):332–335.
- **48** Exelgyn. *Mifepristone Investigators Brochure*. Paris, France: Exelgyn S.A.; 2008.

#### Related resources

Castleman L, Winikoff B, Blumenthal P. Providing abortion in low-resource settings. In: Paul M, Lichtenberg S, Borgatta L, Grimes D, Stubblefield P, Creinin M, eds. *Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care.* Wiley-Blackwell; 2009.

Creinin MD and Gemzell Danielsson K. Medical abortion in early pregnancy. In: Paul M, Lichtenberg S, Borgatta L, Grimes D, Stubblefield P, Creinin M, eds. *Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care.* Wiley-Blackwell; 2009.

Gynuity Health Projects and Reproductive Health Technologies Project (RHTP). Frequently asked questions about fatal infection and mifepristone medical abortion: technical version [fact sheet]. New York: Gynuity Health Projects and RHTP; 2006. Available at: www.gynuity.org/ resources/info/faqs-on-fatal-infection-and-medical-abortiontechnical-version/. **Also available in Spanish and Turkish.** 

Hyman AG, Castleman LD. *Woman-centered abortion care: Reference manual*. Chapel Hill, NC: Ipas; 2005. Available at: www.ipas.org/Publications/Woman-centered\_abortion\_ care\_Reference\_manual.aspx. **Also available in French, Portuguese, and Spanish.** 

Hyman AG, McInerny T, Turner K. *Woman-centered abortion care: Trainer's manual.* Chapel Hill, NC: Ipas; 2005. Available at: www.ipas.org/Publications/Woman-centered\_abortion\_ care\_Trainers\_manual.aspx. **Also available in French, Portuguese, and Spanish.** 

Ibis Reproductive Health. *Medication Abortion:* A Training Module for Health Professionals. Cambridge, MA: Ibis Reproductive Health; 2003. Available at: www.ibisreproductivehealth.org/downloads/Medication\_ Abortion\_Training\_Module.ppt. **Also available in Arabic.**  International Consortium for Medical Abortion (ICMA). *The ICMA Information Package on Medical Abortion: Information for Health Care Providers*. Available at: www.medicalabortionconsortium.org/articles/for-healthcare-providers/. **Also available in Arabic, French, Hindi, Portuguese, Romanian, Russian, and Spanish.** 

Ipas. Best practices in medical abortion: starting contraception after first-trimester abortion [fact sheet]. Chapel Hill, NC: Ipas; 2007. Available at: www.ipas.org/ Publications/asset\_upload\_file685\_2890.pdf.

Also available in German, Russian, and Spanish.

McInerny T, Baird TL, Hyman AG, Huber AB. *A Guide to Providing Abortion Care*. Chapel Hill, NC: Ipas; 2001. Available at: www.ipas.org/Publications/asset\_upload\_file207\_2447.pdf. **Also available in Romanian and Russian.** 

Paul M, Stewart FH, Weitz TA, Wilcox N, Tracey JM. *Early Abortion Training Workbook*. San Francisco, CA: University of California, San Francisco Center for Reproductive Health Research & Policy; 2003. Available at: www.teachtraining.org/ Workbook.html.

Philip NM, Shannon C, Winikoff B, eds. *Misoprostol and Teratogenicity: Reviewing the Evidence*. New York: Gynuity Health Projects and Population Council; 2003. Available at: www.gynuityorg/resources/info/misoprostol-and-teratogenicity-reviewing-the-evidence/. **Also available in Spanish.** 

Talluri-Rao S, Baird TL. *Information and Training Guide for Medication-Abortion Counseling*. Chapel Hill, NC: Ipas; 2003. Available at: www.ipas.org/Publications/asset\_upload\_ file24\_2449.pdf. **Also available in Portuguese and Russian**.