20th Expert Committee on the Selection and Use of Essential Medicines
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PROPOSAL FOR THE INCLUSION OF MISOPROSTOL IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

Submitted on behalf of:

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1. Summary Statement of the proposal for inclusion, change or deletion

The data presented in the following report show that misoprostol is a safe, effective, and low cost option to treat postpartum hemorrhage (PPH) attributable to uterine atony. Results from two large, multi-country studies on PPH treatment comparing the efficacy of misoprostol to intravenous oxytocin, the gold standard for PPH treatment, confirmed that misoprostol effectively controlled excessive bleeding postpartum for 9 out 10 women suffering a hemorrhage (Winikoff 2010; Blum 2010). A recent Cochrane review on the treatment of primary PPH concluded that while oxytocin infusion works better than misoprostol, misoprostol can be used in settings where refrigeration and infusions are not readily available (Mousa 2014). This is relevant as recent research on uterotonic access has shown that even when oxytocin is available, shortages of syringes, needles, and IV infusion sets limit its proper use (Bazant 2013). Further, in many settings the quality of oxytocin is compromised as oxytocic products are often stored at room temperature, although refrigeration is necessary. In one study, 89% of the tested oxytocin and ergometrine ampoules did not meet the specifications for the active ingredient (Stanton 2012).

Recognizing the challenges of making oxytocics available in all settings, in January 2014, the European Medicines Agency approved the first misoprostol product (Hemoprostol) for the treatment of PPH. Hemoprostol contains the active ingredient misoprostol and is manufactured by Linepharma, France. Following an in-depth review of the evidence, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive scientific opinion of Hemoprostol for the treatment of PPH in accordance with Article 58 of Regulation (EC) No. 726/2004. The approved dose is 800µg (200µg x 4 tablets) to be taken sublingually for treatment of PPH due to uterine atony where intravenous oxytocin is not available. The regulatory authorities decided that, although less effective than oxytocin, Hemoprostol has been shown to be safe and of benefit in the treatment of women with PPH and concluded this benefit outweighs any side effects associated with the drug, including transient shivering and fever, which commonly occur following its postpartum administration. Because of oxytocin's widespread availability within the European Union, Hemoprostol is intended for sale only in markets outside the EU, where it is often less possible to provide oxytocin as cold storage and intravenous administration may not be feasible (EMA website).

The literature and the approval by the EMA are consistent with the international guidelines on treatment of PPH. In its 2012 recommendations on the Prevention and Treatment of Postpartum Hemorrhage, the World Health Organization (WHO) noted: *"Intravenous oxytocin is the recommended uterotonic drug for the treatment of PPH; however, in settings where IV oxytocin is not available, or if the bleeding does not respond to oxytocin, the use of intravenous ergometrine, oxytocin-ergometrine fixed dose, or a prostaglandin drug (including sublingual misoprostol, 800 µg) is recommended."* In 2014, the International Federation of Gynecologists and Obstetricians (FIGO) and International Confederation of Midwives (ICM) issued a joint statement on 'misoprostol for the treatment of postpartum haemorrhage in low resource settings' that highlighted the important role of misoprostol in treating postpartum hemorrhage (ICM-FIGO 2014). Indeed in 2012, in its guidelines on PPH, FIGO recognize that in the event that there is no skilled birth attendant present, misoprostol may be the only option available to control PPH and state that research has demonstrated that misoprostol significantly reduces the need for additional interventions for PPH, and hence a dose of misoprostol 800 µg (4×200-µg tablets)

administered sublingually is a safe and effective treatment for PPH due to uterine atony (FIGO 2012).

Misoprostol is already included on the **WHO Model List of Essential Medicines (22.1 Oxytocics)** because of its proven safety and efficacy for medical abortion (following mifepristone), the prevention of postpartum hemorrhage, management of incomplete abortion/miscarriage and induction of labor. We propose that the medicine be specifically listed for its PPH treatment indication in section 22.01.00.00 "Oxytocics" of the WHO List of Essential Medicines (EML) list.

This proposal is based on the following evidence and considerations, described in detail below:

1. 800 μgμg sublingual misoprostol is an easy-to-use evidence-based regimen that can be used in situations in which intravenous oxytocin is not feasible.

2. PPH is one of the largest contributors to maternal morbidity and mortality in low resource countries and accounts for nearly one quarter of all maternal deaths worldwide. The time to death from onset of PPH is two hours (Maine 1993). Prompt initiation of treatment is instrumental in preventing death. Despite receiving prophylaxis, up to 16% women will go on to experience a PPH and require timely treatment (Dabash 2012; Souza 2013). Inclusion of misoprostol for its PPH treatment indication on the EML will bolster the package of interventions available to providers seeking to treat this condition, especially in settings where administration of oxytocin is not feasible.

3. International agencies and governing bodies have recognized the important role that misoprostol can play in the treatment of PPH and have revised their guidelines to reflect this. Inclusion of misoprostol for its PPH treatment indication on the EML will help harmonize the Model List of Essential Medicines with these guidelines and assist countries to adopt and follow standardized guidelines
   - The **WHO Recommendations for the Prevention and Treatment of Postpartum Hemorrhage** (2012) recommend a prostaglandin drug (including sublingual misoprostol, 800 μg) for treatment of PPH if intravenous oxytocin is unavailable or if the bleeding does not respond to oxytocin.
   - **FIGO** has called upon national regulatory agencies and policy makers to approve misoprostol for PPH prevention and treatment (FIGO 2012).
   - **ICM** recommends a single dose of misoprostol 800 μg sublingually for treatment of PPH when 40 IU IV infusion oxytocin is not immediately available (irrespective of the prophylactic measures) (ICM-FIGO 2014).

4. In 2014, the Committee for Medicinal Products for Human Use (CHMP) of the **European Medical Agency (EMA)** approved 800 μg sublingual misoprostol (Hemoprostol) to be used to treat PPH caused due to uterine atony.

5. Misoprostol is safe. Side effects, when they occur, are transient and can be easily managed by providers. In the context of having a PPH, the benefit of having a treatment such as misoprostol outweighs the discomfort associated with short-lived side effects.

2. Name of the focal point in WHO submitting or supporting the application

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3. Name of organization(s) consulted and/or supporting the application

Gynuity Health Projects, New York, USA

4. International Nonproprietary Name (INN, generic name) of the medicine

The International Nonproprietary Name Modified (INNM) of the medicine is misoprostol

5. Formulation proposed for inclusion; including adult and pediatric (if appropriate)

200 μg tablets

6. International availability – sources, of possible manufacturers and trade names

Misoprostol is widely available throughout the world. The first patent was granted in the United States held by Searle (now Pfizer), for marketing of Cytotec®, which continues to be the most widely distributed misoprostol tablet. The drug has been off-patent for several years and is currently manufactured by companies worldwide.

Hemoprostol, the first approved misoprostol product for the treatment of PPH, is manufactured by Linepharma, France and is available for distribution outside of the European Union. In January 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive scientific opinion of Hemoprostol for the treatment of PPH in accordance with Article 58 of Regulation (EC) No. 726/2004. The EMA's Committee for Medicinal Products for Human Use provides opinions on medicines that are not intended for use in the European Union but are needed to prevent or treat diseases of major public health importance around the world. Approval under Article 58 allows European pharmaceutical companies to market high quality products outside of the European Union. While intravenous oxytocin remains the gold standard for PPH treatment and is widely accessible within the EU, it is not always possible to provide this treatment in low resource settings where cold storage and intravenous administration may not be feasible. Hemoprostol was found to have a favorable cost-benefit in low-income settings and is intended solely for markets outside the EU. Detailed recommendations for the use of the product Hemoprostol can be found on the EMA website.

Several misoprostol products have been specifically registered for obstetric indications by export manufacturers Gymiso (Linepharma) (Acme Formulations (India), Cipla Pharmaceuticals (India), Sigma Pharmaceuticals (Egypt), Square Pharmaceuticals (Bangladesh), Zizhu Pharmaceuticals (China), and Fourtts Laboratories (India)) (Misoprostol product brief: Reproductive Supplies Coalition). A partial list of local manufacturers is shown in **Appendix A.**

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

We request that misoprostol be listed as an individual medicine with multiple therapeutic uses in obstetrics and gynecology. Misoprostol is already included on the **WHO Model List of Essential Medicines (22.1 Oxytocic)** because of its proven safety and efficacy for prevention of postpartum hemorrhage, early medical abortion (with mifepristone), management of incomplete abortion/miscarriage, and induction of labor.

8. Information support the public health relevance

8.1 Disease Burden

It is estimated that in 2013, 289,000 women died during and following pregnancy and childbirth (Table 1,WHO 2014). Hemorrhage accounts for over one quarter of these maternal deaths making it the most common direct cause of death among women and one of the main causes of maternal mortality globally (Say 2014). PPH is a largely unpredictable condition following childbirth and two-thirds of PPH cases occur in women with no known risk factors (Mousa 2008).

Maternal deaths from PPH often involve delays in seeking and receiving appropriate care (Souza 2013). The burden of maternal mortality falls most heavily on low resource countries where 99% of maternal deaths occur (Table 1, WHO 2014). This disparity is largely attributable to the greater likelihood of deliveries unattended by trained personnel and limited access to care, including uterotonic drugs that require administration by skilled providers.

Indeed, the risk of dying from PPH is 100 times higher in developing countries than in developed countries (Ramanathan and Arulkumaran 2006). A systematic review of studies documenting causes of maternal death, found that hemorrhage was the leading cause of death in Southern Asia (> 30% of deaths) and the second leading cause of death in Sub-Saharan Africa (>24% of deaths) (Table 2, Say et al 2014). Further, PPH can exacerbate existing anemia and possibly necessitate blood transfusion and surgical care with their associated risks. Given that the average time to death from onset of PPH is two hours (Maine 1993) and that PPH may contribute to severe morbidity following childbirth, it is important that delivery care attendants have access to all evidence-based interventions, including misoprostol, to treat PPH immediately.

Table 1 Estimates of maternal mortality ratio, number of maternal deaths, and lifetime risk, by United Nations MDG region, 2013 (WHO 2014)

Region	MMR[a]	Range of MMR uncertainty		Number of maternal deaths[a]	Lifetime risk of maternal death[a] 1 in:
		Lower estimate	Upper estimate		
World	210	160	290	289 000	190
Developed regions[b]	16	12	23	2300	3700
Developing regions	230	180	320	286 000	160
Northern Africa[c]	69	47	110	2700	500
Sub-Saharan Africa[d]	510	380	730	179 000	38
Eastern Asia[e]	33	21	54	6400	1800
Eastern Asia excluding China	54	35	97	480	1200
Southern Asia[f]	190	130	280	69 000	200
Southern Asia excluding India	170	110	270	19 000	210
South-eastern Asia[g]	140	98	210	16 000	310
Western Asia[h]	74	50	120	3600	450
Caucasus and Central Asia[i]	39	31	53	690	940
Latin America and the Caribbean	85	66	120	9300	520
Latin America[j]	77	59	110	7900	570
Caribbean[k]	190	130	310	1400	220
Oceania[l]	190	100	380	510	140

[a] The MMR, number of maternal deaths, and lifetime risk have been rounded according to the following scheme: <100, no rounding; 100-999, rounded to nearest 10; 1000-9999, rounded to nearest 100; and >10 000, rounded to nearest 1000.
[b] Albania, Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, Montenegro, The Netherlands, New Zealand, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, The former Yugoslav Republic of Macedonia, Ukraine, United Kingdom of Great Britain and Northern Ireland, United States of America.
[c] Algeria, Egypt, Libya, Morocco, Tunisia.
[d] Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cabo Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.
[e] China, Democratic People's Republic of Korea, Mongolia, Republic of Korea.
[f] Afghanistan, Bangladesh, Bhutan, India, Iran (Islamic Republic of), Maldives, Nepal, Pakistan, Sri Lanka.
[g] Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, The Philippines, Singapore, Thailand, Timor-Leste, Viet Nam.
[h] Bahrain, Iraq, Jordan, Kuwait, Lebanon, Occupied Palestinian Territory, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Turkey, United Arab Emirates, Yemen.
[i] Armenia, Azerbaijan, Georgia, Kazakhstan, Tajikistan, Turkmenistan, Uzbekistan.
[j] Argentina, Belize, Bolivia (Plurinational State of), Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, Venezuela (Bolivarian Republic of).
[k] Bahamas, Barbados, Cuba, Dominican Republic, Grenada, Haiti, Jamaica, Puerto Rico, Saint Lucia, Saint Vincent and the Grenadines, Trinidad and Tobago.
[l] Fiji, Kiribati, Micronesia (Federated States of), Papua New Guinea, Samoa, Solomon Islands, Tonga, Vanuatu.

Table 2 Distribution of deaths caused by hemorrhage by region (Say et al 2014)

	Hemorrhage
Developed countries	16.3 (11.1–24.6)
Sub-Saharan Africa	24.5 (16.9–34.1)
Southern Asia	30.3 (14.0–54.8)
Latin America / Caribbean	23.1 (19.7–27.8)

8.2 Treatment of PPH

Uterine atony, or failure of the uterus to contract after delivery, is the most common cause of PPH and accounts for up to 90% of PPH cases (Mousa 2001; Carroli 2008). Administration of prophylactic uterotonics has been shown to reduce bleeding after delivery (Begley 2011), but does not eliminate the need for treatment for all women. Approximately, 3-16% of women are still at risk of developing a PPH (Carroli 2008; Mobeen 2011). Although excessive blood loss is largely preventable, and in most cases can be easily managed when it occurs, early recognition and timely administration of uterotonics are critical steps to avoiding severe outcomes and complications associated with this condition. Effective uterotonic management of PPH can avoid recourse to more complex and invasive interventions, including blood transfusion and surgical techniques for controlling blood loss. Further, early use of second line therapies, including additional uterotonics, may reduce the need for more invasive procedures (Chan 2013).

Oxytocin, administered intravenously, is recommended to treat PPH caused by uterine atony because it is safe and highly effective and free of the side effects, in comparison with other uterotonics, such as ergometrine, (WHO 2012). However its routine use for this indication is complicated by the need for cool storage, sterile equipment, and skilled personnel – all requirements for its optimal administration. A recent Cochrane review on the treatment of primary PPH concluded that while oxytocin infusion works better than misoprostol, misoprostol can be used in settings where refrigeration and infusions are not readily available (Mousa et al 2014). Indeed this conclusion is reflected in WHO and FIGO clinical guidelines on PPH. In the event that IV oxytocin is not available, both organizations recommend use of 800 μg sublingual misoprostol to treat of PPH due to uetrine atony (FIGO 2012; WHO 2012).

While efforts must be made to make intravenous oxytocin available for use, in settings where use of oxytocin infusion is not feasible or when it does not work as the first-line treatment, an alternate mode of treatment (such as misoprostol) must be made available.

8.3 Assessment of Current Use

Misoprostol has long been considered a promising medicine to treat PPH because of its known ability to induce uterine contractions. While intravenous oxytocin is the standard drug for treatment of PPH and it and other injectable uterotonics, are increasingly available across health systems worldwide, their availability alone does not ensure appropriate use or that high quality products are available for administration. Several recent studies exploring uterotonic access, correct administration, and product quality have shown poor provider knowledge and adherence to protocols and low quality of oxytocic products (Stanton 2012; Stanton 2013). Even in facilities where oxytocin is available, supply shortages of syringes, needles, and IV infusion sets have been identified as barriers to providing appropriate care (Bazant 2013). Oxytocin has also

been commonly found to be stored at room temperature in the facilities visited (Stanton 2012; Stanton 2013). One study testing the chemical potency of oxytocin and ergometrine ampoules found low levels of the active ingredients; 89% of the tested ampoules did not meet the specifications for the active ingredient (Stanton 2012).

To better combat PPH in settings where cool storage and properly equipped skilled personnel are not always available, providers have sought alternative and additional ways to treat this condition. Indeed, misoprostol is widely recognized as a therapeutic alternative to oxytocin or as a second-line agent, and it is commonly included in hospital protocols/algorithms as a pharmacological treatment option for the management of PPH, including in hospitals from both high and low income countries (Shields 2014; Bischofberger 2011; Schlembach 2014; Varatharajan 2011; Sheikh 2011; Lappen 2013). In 2011, a panel of international experts, including obstetricians, gynecologists, hematologists, and anesthesiologists, reviewed current evidence on interventions used to manage postpartum hemorrhage and developed consensus recommendations for the treatment of PPH. The algorithm that was agreed upon includes the use of misoprostol. They explain: "Uterotonics used may vary between institutions and should be patient specific; typical uterotonic administration will include IV infusion of syntocinon, intramuscular syntometrine, or prostaglandin analogues, for example, misoprostol, carboprost, or sulprostone" (Abdul-Kadir 2014). More recently, an expert group, with representatives from 3 countries – Austria, Germany, and Switzerland, was formed to develop a consensus algorithm for managing PPH that could be used for local adaptation. 800 μg (sublingual/rectal) misoprostol is included in the PPH algorithm and recommended for use in cases that do not respond to first-line uterotonics (Girard 2014).

There is no evidence that suggests that revising clinical protocols to allow treatment of PPH with misoprostol or recommendations in support of misoprostol have discouraged the use of oxytocin when available or hampered efforts to promote institutional deliveries in low resource settings.

8.4 Target Population

Provision of misoprostol could positively impact maternal health outcomes after PPH attributable to uterine atony as it would better equip providers to manage PPH in situations where:

- there is a stock-out of oxytocin.
- postpartum bleeding does not respond to oxytocin.
- inadequate infrastructure results in loss of refrigeration thereby compromising the quality of oxytocin.
- social, economic, and geographic constraints prevents access to quality oxytocin products.
- access to additional supplies (IV equipment or skills) necessary for administration of oxytocin are unavailable.

9. Treatment details

9.1 Dosage regimen and duration

For PPH treatment, a single dose of 800 µg (4 tablets of 200 µg) sublingually, administered upon diagnosis of excessive postpartum bleeding suspected to be due to uterine atony, is recommended based on evidence from clinical trials (Winikoff et al 2010; Blum et al 2010; WHO 2012; FIGO 2012; ICM 2014).

In treating PPH, rapid induction of uterine contractions is desirable and is best achieved through the sublingual route which achieves a rapid onset of action, prolonged activity, and greater bioavailability, as opposed to other routes of administration (Chong 2004; Tang 2002; Zieman 1997; Mousa 2014). The sublingual route has been used in several clinical studies of misoprostol for PPH treatment (Winikoff 2010; Blum 2010; Zuberi 2008; Widmer 2010). In the two large RCTs, misoprostol administered by the sublingual route controlled postpartum hemorrhage within 20 minutes for 9 out of 10 women (Winikoff 2010; Blum 2010).

There are no large, double-blind randomized trials with adequate power testing any other route (Mousa 2014). When misoprostol is taken sublingually, the woman holds the pills under her tongue for 20 – 30 minutes. Any remaining pill fragments can be swallowed. This route is easy for providers and feasible for women. Studies have shown that women are satisfied with sublingual administration of misoprostol and have little difficulty holding the pills under their tongues (Winikoff 2010; Blum 2010).

9.2 Reference to Existing WHO and Other Clinical Guidelines

Several large international bodies, including the WHO, FIGO, and ICM have updated their guidelines to reflect the current body of evidence. The guidelines recognize that misoprostol may be the only option available to control PPH in the event that oxytocin is unavailable. Table 3 summarizes current recommendations and guidelines from several key organizations.

Bohlmann et al conducted a review of national and international guidelines on the medical management of PPH to examine the consistency of recommendations for different uterotonics. They noted that misoprostol is discussed in national and international guidelines as an uterotonic alternative especially in low resource settings. Although it is not the first choice uterotonic, the authors summarize that "it may be a life-saving option in a home-birth setting when no IV access is available or in women with severe hypertension or asthma when other prostaglandins are contraindicated" (Bohlmann 2014).

Table 3 List of selected clinical guidelines on misoprostol for PPH treatment

Agency (Date) *Document*	**Guidelines**
International Confederation of Midwives (ICM) and International Federation of Gynecology and Obstetrics (FIGO) (2014) *Joint Statement, Misoprostol for the treatment of postpartum haemorrhage in low resource settings*	Single dose of misoprostol 800 µg sublingually is indicated for treatment of PPH when 40 IU IV infusion oxytocin is not immediately available (irrespective of the prophylactic measures)
American Congress of Obstetricians and Gynecologists (2006, reaffirmed 2013) *ACOG Practice Bulletin*	Misoprostol is included in the list of uterotonics to be used as the first-line treatment for hemorrhage in the event of decreased uterine tone.
La Federación Latinoamericana de Sociedades de Obstetricia y Ginecología (FLASOG) (2013) *Uso de Misoprostol en Obstetricia y Ginecología.*	800 µg sublingual misoprostol is recommended for PPH treatment when oxytocin is not available.
WHO (2012) *Recommendations for the prevention and treatment of postpartum haemorrhage*	IV oxytocin alone is the recommended uterotonic drug for the treatment of PPH. If IV oxytocin is unavailable, or if the bleeding does not respond to oxytocin, the use of intravenous ergometrine, oxytocin-ergometrine fixed dose, or a prostaglandin drug (including sublingual misoprostol, 800 µg) is recommended.
International Federation of Gynecology and Obstetrics (2012) *FIGO Guidelines: Treatment of postpartum hemorrhage with misoprostol*	Single dose of misoprostol 800 µg sublingually is indicated for treatment of PPH when 40 IU IV oxytocin is not immediately available (irrespective of the prophylactic measures).
International Federation of Gynecology and Obstetrics, FIGO Safe Motherhood and Newborn Health Committee (Lalonde, FIGO 2012) *FIGO Guidelines: Prevention and treatment of postpartum hemorrhage in low-resource settings*	• Includes a call to action that all birth attendants have the necessary training—appropriate to the settings where they work—to administer uterotonic drugs safely and ensure that uterotonics are available in sufficient quantity to meet the need. To achieve this, they call upon national regulatory agencies and policy makers to approve misoprostol for PPH prevention and treatment. • Guidelines noted that in home births without a skilled attendant, misoprostol may be the only technology available to control PPH.
Royal College of Obstetricians and Gynaecologists (2009, updated 2011) *Postpartum Haemorrhage, Prevention and Management (Green-top Guideline No. 52)*	• Misoprostol may be an appropriate alternative (for PPH treatment) in settings where parenteral prostaglandins are not available or where there are contraindications (usually asthma) to prostaglandin F2. • If uterine atony perceived to be the cause of the bleeding, a series of mechanical and pharmacological measures (including misoprostol) should be instituted.
Society of Obstetricians and Gynaecologists of Canada (SOGC) (Leduc 2009) *Active Management of the Third Stage of Labour: Prevention and Treatment of Postpartum Hemorrhage*	Misoprostol (off-label use) is included in the list of uterotonics to be administered for PPH caused by uterine atony: • 400 to 800 µg. Onset of effects is faster with oral or sublingual than with rectal administration. • 800 to 1000 µg. Effects are longer lasting with rectal than with oral administration.

10. Summary of comparative effectiveness in a variety of clinical settings

For over a decade, researchers have tried to determine if there is an association between postpartum administration of misoprostol and cessation of excessive blood loss. A Pub Med review of misoprostol for PPH treatment in English, Spanish or French literature through October 2014 found eight randomized controlled trials (RCTs) and ten other reports. Of the eight RCTs of postpartum administration of misoprostol for treatment of PPH three compared misoprostol to standard uterotonics alone, four studied the potential adjunct effect of misoprostol when combined with standard uterotonics for PPH treatment, and one compared misoprostol to IV tranexamic acid. (Winikoff 2010; Blum 2010; Widmer 2010; Walraven 2005; Hofmeyr 2005; Zuberi 2008; Lokugamage 2001; Sahhaf 2014).

a. Trials of misoprostol alone to treat PPH

Four published RCTs assess the role of misoprostol when used alone for treatment of PPH.

The two largest multi-center, large-scale double-blinded, placebo-controlled, randomized trials compared the effectiveness, safety, and acceptability of 800 μg sublingual misoprostol to 40 IU intravenous oxytocin among 1,786 women diagnosed with PPH after vaginal delivery due to suspected uterine atony (Blum 2010; Winikoff 2010).

Among women receiving oxytocin prophylactically, misoprostol stopped bleeding as rapidly as oxytocin did and with a similar quantity of blood loss. Among women who did not receive a prophylactic uterotonic, oxytocin was significantly better at treating PPH. These findings demonstrate that, relative to oxytocin, misoprostol is also effective in controlling post-partum bleeding. In both trials, whether treatment was with oxytocin or misoprostol, nine out of ten women had their bleeding successfully controlled within 20 min of drug administration (tables 4 -5).

A trial by Lokugamage et al reported that 800 μg rectal misoprostol conferred a significant advantage over syntometrine and IV syntocinon for PPH treatment. Reporting on 64 women treated for postpartum hemorrhage, the authors found a 28.1% difference in the rate of bleeding cessation in 20 minutes in favor of misoprostol (p=0.01). However, the study was not blinded and blood loss was assessed visually, which may have permitted investigator bias (Lokugamage 2001, tables not shown).

A trial by Sahhaf et al compared treatment of abnormal PPH with tranexamic acid (TXA) to misoprostol. In this trial, 200 women were randomized to receive either TXA through intravenous infusion or 1000 μg misoprostol administered rectally. Haemoglobin levels, measured 6-12 hours after delivery, were similar in both groups [8.9 vs. 9 (p =0.22)] in the TXA and misoprostol groups, respectively (Sahhaf 2014, tables not shown).

b. Trials of misoprostol as adjunct PPH treatment

Four RCTs and one retrospective cohort study reported on misoprostol as an adjunct to standard PPH treatments (Tables 6-9) (Walraven 2005; Hofmeyr 2005; Zuberi 2008; Baruah 2008; Widmer 2010). The initial trials were not adequately powered to detect significant differences

between the misoprostol and placebo arms but all showed favorable trends in blood loss reduction in the misoprostol arms leading to calls for a larger adequately powered trials to definitively determine the role of misoprostol as adjunct care for PPH (Hofmeyr 2004; Walraven 2004; Zuberi 2008).

A trial by Widmer et al enrolled 1422 women at hospitals in five countries and randomized them to misoprostol plus standard uterotonics or placebo plus standard uterotonics. In this trial, women in both study arms had similar rates of additional blood loss ≥500 mL at 60 min [misoprostol plus standard uterotonics: 14·2% (100/705) vs. placebo plus standard uterotonics: 14·0% (100/717), relative risk RR 1·02, 95%, CI 0·79 - 1·32]. Misoprostol was associated with a significantly higher incidence of shivering [misoprostol plus standard uterotonics: 64·6% (455/704) vs. placebo plus standard uterotonics: 32·1% (230/717) RR: 2·01 95% CI 1·79 - 2·27]. These findings demonstrate that the addition of 600 µg sublingual misoprostol to conventional injectable uterotonics for PPH treatment confers no clinical advantage. Meta-analysis of blood loss ≥500 mL reported in the four trials on adjunct PPH treatment with misoprostol show a pooled risk ratio of 0·89 (95% CI 0·71-1·12) (Widmer 2010).

A retrospective cohort study examined data from 58 patients with PPH receiving either misoprostol or methylergonovine malaete as second line treatment (after standard oxytocics) for primary PPH. The results showed similar outcomes in terms of need for third line treatment to stop PPH (misoprostol = 67%, methylergonovine malaete = 77%) and other interventions (no statistically significant differences between need for blood transfusion, third line medical treatment or surgery) (tables not shown). This study offers some information about possible utility of misoprostol as adjunct/second line PPH treatment but its design introduces possible selection bias and its small number (n=58) makes it difficult to draw firm conclusions about the generalizability of the results (Baruah 2008).

c. Case reports and observational studies

Eight reports tested a range of misoprostol doses (200 µg to 1000 µg) and different routes of administration with or without other uterotonics (Mousa 2007; O'Brien P et al 1998; Ozan H 2000; Abdel-Aleem H 2001; Shojai 2004; Shojai 2001; Adekanmi 2001; Oboro VO 2003; León 2012) (Table 10).

Table 10 also highlights two additional studies. In an open-label one arm study investigating 800 µg sublingual misoprostol as first-line treatment of primary PPH due to uterine atony, blood loss was controlled, without any recourse to additional uetrotonic drugs or interventions in 84.7% (111/131) women (Okonofua 2014). An ecological community-based study compared referral rates in districts where misoprostol was available for PPH treatment versus those in which it was not. The study showed that fewer than 2% of the women with PPH in the intervention area were referred for higher level care compared with 19% in the non-intervention area (Prata 2005).

d. Summary of effectiveness from clinical trials

Since three review papers were published in 2007 concluding that there was insufficient evidence on misoprostol for PPH treatment (Blum 2007; Gülmezoglu 2007; Mousa 2007), additional evidence has been generated that suggest otherwise. Two published large randomized controlled trials demonstrate that while oxytocin remains the gold standard for PPH treatment,

misoprostol is also effective in controlling post-partum bleeding (Winikoff 2010; Blum 2010). In 2012, an expert review covering evidence from seven randomized controlled trials for treatment of PPH summarized the body of evidence in support of misoprostol for treatment of PPH and determined that it can fill a service delivery gap (Sheldon 2012).

A recent Cochrane review on the treatment of PPH, noted that treatment with misoprostol, as compared with IV oxytocin, or combined oxytocin and ergometrine, or placebo, does not yield any statistical significant differences in clinical outcomes (maternal mortality serious maternal morbidity, admission to intensive care and hysterectomy). Treatment with IV oxytocin resulted in fewer cases with blood loss greater than 1000ml or that required additional uterotonics to control bleeding. The authors concluded that while the current evidence suggests that misoprostol is less effective than oxytocin, in the absence of oxytocin, misoprostol can be used for treatment of PPH caused due to uterine atony (Mousa 2014).

While there appears to be no advantage to adjunct use of misoprostol for PPH treatment, use of misoprostol alone for PPH treatment is effective in controlling PPH and can confer significant benefits in settings where access to other uterotonics (such as oxytocin or ergometrine) is not feasible.

10.1 Randomized controlled trials testing the effect of misoprostol to treat PPH

Table 4 Treatment of post-partum PPH with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial (Blum et al, 2010)

	Misoprostol n = 407	Oxytocin n = 402	Relative Risk (95% CI)	p-value
Active bleeding controlled w/in 20 min. with initial uterotonic treatment	363 (89.2)	360 (89.6)	0·99 (0.95–1.04)	.867
Additional blood loss ≥ 300 ml after treatment	139 (34.4)	123 (30.7)	1.12 (0.92–1.37)	.146
Additional blood loss ≥ 500 ml after treatment	58 (14.4)	53 (13.2)	1·09 (0.77–1.54)	.713
Additional blood loss ≥ 1000 ml after treatment	11 (2.7)	3 (0.7)	3.62 (1.02–12.89)	.062
Drop in Hb ≥ 2 g/dL or blood transfusion	152 (37.6)	142 (35.7)	1.06 (0.88–1.27)	.567
Drop in Hb ≥ 3 g/dL or blood transfusion	104 (25.7)	90 (22.6)	1.14 (0.89–1.46)	.301
Additional uterotonics	40 (9.8)	46 (11.5)	0.86 (0.58–1.28)	.260
Blood transfusion	24 (5.9)	18 (4.5)	1.32 (0.73–2.39)	.229
Hysterectomy	4 (1.0)	2 (0.5)	1.98 (0.36–10.73)	.350
Maternal death	1 (0.2)	1 (0.2)	0.99 (0.06–15.74)	.747
Data are n (%) unless otherwise specified. RR = Relative Risk. Hb=Hemoglobin.				

Table 5 Treatment of PPH with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial (Winikoff, et al, 2010)

	Misoprostol (n = 488)	Oxytocin (n = 490)	RR (95% CI)	p-value
Active bleeding controlled within 20 min with initial uterotonic treatment	440 (90.2)	468 (95.5)	0.94 (0.91–0.98)	0.001
Additional blood loss ≥ 300 ml	147 (30.1)	83 (16.9)	1.78 (1.40–2.26)	<0.001
Additional blood loss ≥ 500	53 (10.9)	20 (4.1)	2.84 (1.63–5.01)	<0.0001
Additional blood loss ≥ 1000	5 (1.0)	3 (0.6)	1.67 (0.40–6.96)	0.360
Drop in Hb ≥ 2 g/dL or blood transfusion	250 (51.2)	230 (46.9)	1.09 (0.96–1.24)	0.101
Drop in Hb ≥ 3 g/dL or blood transfusion	199 (40.8)	148 (30.2)	1.35 (1.14–1.60)	<0.0001
Additional uterotonics	61 (12.5)	31 (6.3)	1.98 (1.31–2.99)	0.001
Blood transfusion	41 (8.4)	26 (5.3)	1.58 (0.98–2.55)	0.036
Hysterectomy/Other surgery	0 (0.0)	0 (0.0)	-- --	-- --
Maternal death	0 (0.0)	0 (0.0)	-- --	-- --
Data are n (%) unless otherwise specified. RR = Relative Risk. Hb=Hemoglobin.				

10.2 Randomized-controlled trials (RCTs) testing the adjunct effect of misoprostol when used in conjunction with standard oxytocics to treat PPH

Table 4 Misoprostol as an adjunct to standard uterotonics for treatment of PPH: a multicentre, double-blind randomised trial (Widmer et al, 2010)

	Misoprostol + standard uterotonics (n=705)	Placebo + standard uterotonics (n= 717)	RR (95% CI)
Blood loss of ≥ 500 ml within 60 min after randomization	100 (14)	100 (14)	1.02 (0.79–1.32)
Blood loss of ≥ 1000 ml within 60 min after randomization	9 (1)	9 (1)	1.02 (0.41–2.55)
Blood loss of ≥ 500 ml within 90 min after randomization‡	149 (21)	162 (23)	0.93 (0.77–1.14)
Blood loss of ≥ 1000 ml within 90 min after randomization‡	17 (2)	22 (3)	0.78 (0.42–1.47)
Any uterotonic after randomization	188 (27)	203 (28)	0.94 (0.79–1.11)
Hb concentration of <80 g/l within 24 hours postpartum or need for blood transfusion*	121 (18)	139 (20)	0.89 (0.72–1.11)
Blood transfusion after randomization	103 (15)	117 (16)	0.89 (0.70–1.14)
Maternal death	2 (<1)	0	NA
Severe morbidity§	8 (1)	10 (1)	0.81 (0.32–2.00)
Data are number (%) or median (IQR), unless otherwise indicated. NA=not applicable. **Data were recorded for 691 patients receiving misoprostol and 710 patients receiving placebo; outcomes could not be measured in remaining patients. ‡Data were recorded for 703 patients receiving misoprostol and 714 patients receiving placebo; outcomes could not be measured in remaining patients. §Defined as hysterectomy or admission to a maternal intensive care unit.*			

Table 5 Adjunct Misoprostol for treating PPH: a randomized controlled trial (Hofmeyr et al, 2004)

	Misoprostol + standard uterotonics (n=117)	Placebo + standard uterotonics (n=121)	RR/MD	95% CI
Blood loss 500ml*	6 (5.1)	11 (9.2)	0.56	0.21–1.46
Blood loss ≥ 1,000ml*	1 (0.85)	0 (0)	--	--
24 hour Hb < 8 g/dl or blood transfusion	43 (39)	37 (32)	1.23	0.86–1.75
Additional uterotonic after enrolment	63 (57)	63 (56)	1.01	0.80–1.27
Blood transfusion	19 (17)	15 (13)	1.31	0.70–2.45
Hysterectomy**	3 (2.6)	0 (0)		
Maternal death**	3 (2.6)	0 (0)		

Data are n (%)
*RR = relative risk; MD = mean difference; Conf = confidence; SD = standard deviation *Measured, within 1 hour after enrolment ** One woman died after hysterectomy and is counted in both outcomes*

Table 6 Misoprostol in the treatment of PPH in addition to routine management: a placebo randomised controlled trial (Walraven et al, 2004)

	Misoprostol+ standard uterotonics (n=79)	Placebo+ standard uterotonics (n= 81)	Effect size* (95% CI)
Blood loss ≥ 500 ml	13 (16.5)	23 (28.4)	0.58 (0.32–1.06)
Blood loss ≥ 1000 ml	2 (2.5)	5 (6.2)	0.41 (0.09–1.77)
Postpartum hb <6 g/ dl -1 or blood transfusion	12 (15.2)	12 (14.8)	1.02 (0.49–2.15)
Hysterectomy	0	2 (2.5)	-
Use of additional uterotonics	3	5 (6.2)	0.62 (0.17–2.25)

Data are n(%)
**Relative risk except for average blood loss after taking study medication. For other outcomes, the difference between means is shown.*

Table 7 Misoprostol in addition to routine treatment of PPH: A hospital-based randomized-controlled trial in Karachi, Pakistan (Zuberi et al, 2008)

	Misoprostol + standard uterotonics (n=29)	Placebo + standard uterotonics (n= 32)	RR (95% CI) or p-value
Blood loss ≥ 500 ml post-treatment	7.4 (2)*	12.5 (4)	0.59 [0.12, 2.99]
Mean drop in Hb ± sd (range)	2.0 ± 1.1 (0.4-4.2)	2.2 ± 1.4 (0.1-5.1)	P= .614
Postpartum Hb >/ g/dl lower than pre-delivery Hb	41.4 (12)	56.3 (18)	0.74 [.43, 1.25]
Blood transfusion	17.2 (5)	18.8 (6)	.92 [.31, 2.69]
Referrals for additional PPH care	3.4 (1)	3.2 (1)	1.1 [.07, 16.9]

Data are %(n) unless otherwise specified

**Two cases in the misoprostol arm have incomplete blood loss measurements and were excluded from analysis of measured postpartum blood loss.*

Table 8 Case reports and observational studies on misoprostol for PPH treatment

Author, publication date	Misoprostol Regimen	Women Enrolled	Success±
O'Brien et al, 1998	1000 ug rectally	14	14/14 (100)
Ozan et al, 2000	400 ug orally, repeated 2 hourly once or twice	2	2/2 (100)
Abdel-Aleem et al, 2001	600 ug (n=4) 1000 ug (n=14) rectally soon after other uterotonics	18	1618 (88)
Shojai et al, 2001	200 ug rectally	5	5/5 (100)
Adekanmi et al, 2001	800 ug intrauterine + bimanual compression of uterus	1	1/1 (100)
Oboro et al, 2003	800 ug intrauterine + bimanual compression of the uterus	1	1/1 (100)
Shojai et al, 2004	1000 ug rectally	41	26/41 (63)
Prata el al, 2005	1000 ug rectally	111*	103**/111 (93)
León et al, 2012	800 ug sublingually	50	48/50 (82)
Okonofua et al, 2014	800 ug sublingually	131^	111/131 (84.7)

± *Data are N(%)*

**women delivering vaginally with subsequent blood loss of 500 ml or more in the intervention group*

*** women who did not need to be referred to higher level of care*

^ *women who did not require additional interventions after first line treatment with misoprostol*

Table 9 Comparison of PPH treatment outcomes with 600 and 800 sublingual misoprostol in women receiving prophylactic oxytocin (León et al, 2012; Blum et al, 2010)

	600 µg sublingual misoprostol (n=50)	800 µg sublingual misoprostol (n=407)	RR (95% CI)
Active bleeding controlled within 20 min with initial uterotonic treatment	41 (82.0)	363 (89)	0.92 (0.80–1.05)
Additional blood loss post-treatment, median (IQR)	200 (100, 300)	200 (100-350)	Ns
Additional blood loss ≥ 300 mL post-treatment	13 (26.0)	139 (34)	0.76 (0.47–1.24)
Additional blood loss ≥ 500 mL post-treatment	5 (10.0)	58 (14)	0.70 (0.30–1.67)
Additional blood loss ≥ 1000 mL post-treatment	0 (0.0)	11 (3)	--
Data are n (%) unless otherwise indicated			

11. Summary of comparative evidence on safety

11.1 Side effects after misoprostol

Women who receive misoprostol during the third stage of labor are at risk for elevated body temperature, shivering, nausea and vomiting. The most common side effects associated with the postpartum administration of misoprostol are shivering and pyrexia (Durocher 2010; Elati 2012). Studies on postpartum use of misoprostol show the rates of shivering and fever to be related, and to be dose- and route-dependent (Elati 2011; Elati 2012; Mousa 2014). Temperature above 39°C was observed in 8.3, 8.3, and 45% of women given 200, 400, and 600 µg sublingual misoprostol, respectively (Elati 2011). Higher rates of shivering and elevated body temperature are also associated with oral and sublingual routes of administration, which achieve a higher and quicker maximum plasma concentration than vaginal or rectal administration (Chong 2004; Tang 2002; Zieman 1997). One prevention trial comparing an oral misoprostol versus rectal administration of 600 µg confirmed that the oral dose resulted in significantly higher rates of shivering (76 versus 54%) and fever (9 versus 1%) (Khan 2003).

Shivering and fever are common side effects following misoprostol's use as a first-line treatment and as an adjunct therapy for PPH (see Tables 12-13). Two studies testing an 800 µg dose of sublingual misoprostol for PPH treatment have documented rates of shivering that range from 37 to 47%, compared with a 15% rate of shivering among women given treatment with IV oxytocin. In these studies the rates of fever after treatment were also more common in the misoprostol group (34%) vs. 10% in the oxytocin IV group (Blum 2010; Winikoff 2010). Two studies testing a 600 µg regimen of sublingual misoprostol versus placebo as an adjuvant therapy also report that shivering and fever occurred significantly more often among women randomized to misoprostol (Table 13) (Zuberi 2008; Widmer 2010). Lower rates of shivering and fever were documented in one study testing 600 µg (200 µg orally + 400 µg sublingually) among 160 women randomized to receive either misoprostol + standard uterotonics or placebo + standard uterotonics (shivering 29% vs. 10%; fever 20% vs. 10%) (Walraven 2004). Overall, reported rates of shivering and fever vary greatly in the literature, in part due to the dose and route of misoprostol used to administer the medicine, but also the variation may be explained by methodologies used for measurement, whether systematically assessed or self-reported (Patted

2009; Durocher 2010; Elati 2012). The studies by Okonofua et al (2014) and by Sahhaf et al (2014) report minimal side effects.

In several PPH prevention and treatment studies, misoprostol has been associated with fever greater than 40.0°C (104°F). Cases of high fever noted in the literature include five of 9198 cases reported from the largest hospital- based clinical trial on the prevention of PPH, in which a prophylactic oral dose of 600 micrograms misoprostol was used (Gülmezoglu 2001). Four cases of 1026 were reported by Ng and colleagues after testing a similar regimen (Ng 2001). One case was reported in 1997 by Chong et al. A PPH treatment trial in South Africa reported three women (out of 114) with temperatures of above 40.0°C following 1000 μg misoprostol (200 μg orally + 400 μg sublingually + 400 μg rectally) (Hofmeyr 2004). There have been no other reports of high fever following rectal administration of misoprostol for PPH (Mousa 2007; Khan 2003). In Pakistan, one case of high fever (out of 29) following adjunct treatment with a sublingual dose of 600 μg was reported (Zuberi 2008). A multi-country trial investigating the adjunct use of sublingual misoprostol (600 μg) following standard uterotonics for PPH treatment also documented a 7% rate of high fever above 40.0°C among 48 women (out of 704), compared with a rate of 1% among women who received standard uterotonics + placebo to treat their PPH (Widmer 2010). In addition, a higher-than-expected rate of fever above 40.0°C in one of nine sites (Quito, Ecuador: 36%; 58/163) of a multi-country study of 800 μg regimen of misoprostol for first-line treatment for PPH was reported, whereas much lower rates were recorded in the other eight sites, ranging from 0% to 9% (Blum 2010; Winikoff 2010; Durocher 2010). In all of these hospital-based reports, the elevated temperatures did not result in further complication. A World Health Organization report on the safety profile of misoprostol for obstetrical indications reviewed all the published cases of temperature of 40 °C or higher following treatment with misoprostol for PPH. The authors commented that in all cases temperature resolved itself within several hours and without complication; management was reported with antipyretics and cool compresses (Wannmacher 2010).

To understand better the characteristics of fevers above 40.0°C that occurred at a higher frequency in Quito, Ecuador, systematic measures of body temperature post-treatment with 800 μg of sublingual misoprostol were documented for 58 cases with high fever in this site (Durocher 2010). High fever was typically characterized by a sharp increase in temperature within 1 hour of treatment, a peak temperature 1-2 hours post-treatment, and a gradual decline in temperature over a period of 3 hours. As shown in Figure 1, the pattern of temperature elevation appears to mimic misoprostol blood concentration following sublingual administration and the fevers followed a predictable course.

A follow-up study in Ecuador tested a lower dose of sublingual misoprostol (600 μg) to determine whether the rate of fever could be reduced in this setting (León 2012). This study enrolled women who have been given uterotonics prophylactically. Body temperature was systematically measured for 50 women diagnosed with PPH and given 600 μg of sublingual misoprostol as first-line treatment. Rates of side effects were compared between this study and a previous one testing an 800 μg regimen of sublingual misoprostol among women not exposed to prophylactic uterotonics (table 14). Data on the 800 μg sublingual regimen (table 14) were collected as part of the multi-country RCT comparing treatment with misoprostol to oxytocin (Winikoff 2010). The incidence of high fevers (above 40.0°C) following treatment with 600 μg sublingual misoprostol compared to previously documented rates using 800 μg sublingual misoprostol show a 50% reduction in the rate of high fever with the lower dose (8/50; 16% vs.

58/163; 36%; relative risk 0.45 95% CI 0.23-0.88) (table 15). Only one woman had severe shivering following the 600μg dose, compared with 19 women in the 800 μg cohort (2% vs. 12%; relative risk 0.17 (0.02-1.25)) No cases of delirium/altered sensorium were reported. The temperature trends (see Figure 2) documented in these two studies in Ecuador provide reassurance to clinicians that misoprostol-induced fever (regardless of how high the peak temperature) are transitory.

Blood samples were analyzed from the 50 participants from Quito, Ecuador in the study conducted by León et al. in order to investigate whether genetic variability contributes to misoprostol-induced fever (Alfirevic, RCOG Congress, 2013). These 50 women received 600 μg sublingual misoprostol to treat their PPH and had their body temperature systematically measured. DNA was extracted from whole blood and genotyping for 33 single nucleotide polymorphisms (SNPs) was performed using mass spectrometry (Sequenom). The gene selection was based on mechanisms involved in prostaglandin induced fever, and included genes that encode misoprostol pharmacological targets, enzymes involved in prostaglandin metabolism and proteins involved in transport across body membranes. Statistical analysis was performed using analysis of variance (ANOVA). An association was found between misoprostol-induced fever and SNPs in genes encoding drug transporters. In vitro experiments also confirmed that misoprostol was actively transported across the blood brain barrier by ABCC4. These findings demonstrate that genetic variability in misoprostol transporters may be a contributing factor in misoprostol-induced fever. In addition, this is the first study to demonstrate that misoprostol acid is a substrate for ABCC4, which is expressed at the blood–brain barrier (Alfirevic 2006; RCOG Congress, 2013). The evidence supports the hypothesis that genetic variation may predispose some populations to misoprostol-induced side effects, although the researchers call for further genetic studies to replicate these findings. Further the passage of misoprostol acid through the blood brain barrier helps explain the mechanism of action of fever.

A review of the literature confirms that side effects are transient, short-lived and not life-threatening (Gülmezoglu 2007; Patted et al 2009; Ng 2001; Lumbiganon 2002; Durocher 2010; Mousa 2014). Studies have shown these side effects to be tolerable and transient with a range of doses and routes of administration. In settings such as Southern Asia and Sub-Saharan Africa where maternal mortality is 190 and 510 per 100,000, respectively and where PPH (>30%) is leading direct cause of death, misoprostol's therapeutic effect should outweigh the possible discomfort caused by any side effects.

In two ongoing double-blind placebo-controlled trials in Afghanistan and Pakistan, women who deliver at home with a traditional birth attendant or community health worker, receive misoprostol (600 μg oral) for prevention. If diagnosed with PPH, these women go on to receive misoprostol (800 μg sublingual) or placebo. In these studies, approximately half the women who were diagnosed with PPH received 1400 μg misoprostol within an hour of delivery of the baby. Among all women who received the study treatment, there were no serious adverse events. Further, all reported side effects were easily managed and considered tolerable by the women. The preliminary findings from these studies indicate that misoprostol administered for PPH prevention followed by PPH treatment is safe at the community level (Jehan, ICM 2014).

These preliminary results on safety are consistent with evidence from two recently completed community-based RCTs conducted in Egypt and India. Findings from these studies echo the

literature that use of 800 µg sublingual misoprostol is safe and any associated side effects are easily tolerated. In Egypt, women delivering at home with a midwife or nurse-midwife birth attendant received either 800 µg sublingual misoprostol or placebo for treatment of primary PPH (Hassanein, ICM 2014). In India, women delivering at home or at health sub-centres with an auxiliary nurse midwife received either 600 µg oral misoprostol or 800 µg sublingual misoprostol for postpartum bleeding ≥ 350 ml (Goudar, SAFOG 2014). Among women who received 800 µg sublingual misoprostol, the most common side effect was shivering 65% (22/34), 62% (56/90)); followed by nausea [21% (7/34), 7% (6/90)]; fever [9% (3/34), 8% (7/90)]; and vomiting [6% (2/34), 2% (2/90)] in the Egypt and India studies, respectively. Further, in India, 95% women found side effects to be tolerable.

Table 10 Rates of shivering and fever following first-line PPH treatment with 800 µg regimen of sublingual misoprostol

Winikoff et al, 2010* (Multi-country trial)	**Misoprostol n = 488**	**Oxytocin n = 490**	**Relative Risk (95% CI)**
Shivering	229 (46.9)	82 (16.8)	2·80 (2.25–3.49)
Fever	217 (44.5)	27 (5.5)	8·07 (5.52–11.8)
Temp ≥40·0 C°	66 (13.5)	0 (0.0)	-- --
Blum et al, 2010 (Multi-country trial)	**Misoprostol n =407**	**Oxytocin n=402**	**Relative Risk (95% CI)**
Shivering	152 (37.3)	59 (14.7)	2.54 (1.95–3.32)
Fever	88 (21.6)	59 (14.7)	1.47 (1.09–1.99)
Temp ≥40·0 C°	5 (1.2)	1 (<1)	4.94 (0.58–42.09)

Data are n (%)
**Includes site in Quito, Ecuador where incidence of high rate of fever above 40.0°C (36%; 58/163)*

Table 11 Rates of shivering and fever following treatment with an adjunct dose of sublingual misoprostol (600 µg) *

Widmer et al, 2010 (multi-country)	**Misoprostol n=704**	**Placebo n=717**	**Relative Risk (95% CI)**
Shivering			
Any	455 (64.6)	230 (32.1)	2.01 (1.79–2.27)
Severe	80 (11.4)	7 (1.0)	11.64 (5.41–25.03)
Fever			
≥ 38°C	303 (43)	107 (15)	2.88 (2.37–2.5)
≥ 40°C	18 (3)	3 (<1)	6.11 (1.81–20.65)
Walraven et al, 2004 (The Gambia)	**Misoprostol ^ n=79**	**Placebo n= 81**	**Relative Risk (95% CI)**
Shivering			
Any	23 (29.1)	8 (9.9)	2.95 (1.40–6.19)
Fever			
≥ 37.5°C	16 (20.3)	8 (9.9)	2.05 (0.93–4.52)
Zuberi et al, 2008 (Pakistan)	**Misoprostol n=29**	**Placebo n=32**	**Relative Risk (95% CI)**
Shivering			
None	14 (48.3)	30 (93.8)	
Mild or moderate	11 (37.9)	2 (6.2)	8.28 [2.1–33.1]
Severe	4 (13.8)	0 (0.0)	
Fever			
None	48.3 (14)	90.6 (29)	
Mild or moderate	41.4 (12)	9.4 (3)	5.52 [1.8–17.1]
Severe	10.3 (3)	--	

Data are in n (%)
[*] *Misoprostol plus standard uterotonics versus placebo plus standard uterotonics*
^ *Misoprostol regimen was administered as 400 µg sublingual + 200 µg oral.*

Figure 1 Mean misoprostol plasma concentrations after sublingual administration of misoprostol (800 micrograms), and mean temperatures over time of 58 cases of high fever following treatment with 800 µg sublingual misoprostol in Quito, Ecuador (Durocher et al, 2010)

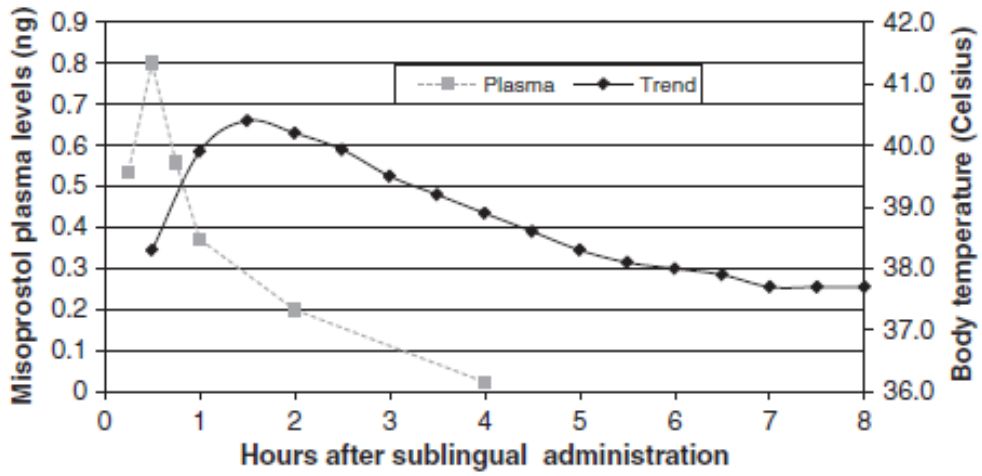


Table 12 Comparison of reported side effects (by provider) among Ecuadorian women given PPH treatment with sublingual misoprostol (600µg and 800µg)^

	600 µg * (n=50)	800 µg ** (n=163)	RR 95% CI
Any fever	44 (88.0)	151 (92.6)	0.95 (0.85–1.06)
≤ 37.9 °C	6 (12.0)	12 (7.4)	1.63 (0.64–4.12)
38.0 – 38.9 °C	23 (46.0)	32 (19.6)	2.34 (1.52–3.61)
39.0 – 39.9 °C	13 (26.0)	61 (37.4)	0.69 (0.42–1.15)
≥ 40.0 °C	8 (16.0)	58 (35.6)	0.45 (0.23–0.88)
Any shivering	48 (96.0)	146 (89.6)	1.07 (0.99–1.16)
Mild shivering	29 (58.0)	56 (34.4)	1.69 (1.23–2.32)
Moderate shivering	18 (36.0)	71 (43.6)	0.83 (0.55–1.24)
Severe shivering	1 (2.0)	19 (11.7)	0.17 (0.02–1.25)
Any fainting	2 (4.0)	4 (2.5)	1.63 (0.31–8.64)
Any nausea	0 (0.0)	8 (4.9)	--
Any vomiting	0 (0.0)	8 (4.9)	--
Any diarrhea	0 (0.0)	2 (1.2)	--
Any other side effect	1 (2.0) ☼	20 (12.3) ☼☼	0.16 (0.02–1.18)

^Rates of side effects were compared between two separate studies testing two different regimens of misoprostol for treatment of PPH among Ecuadorian women with PPH enrolled at a maternity hospital in Quito, Ecuador.

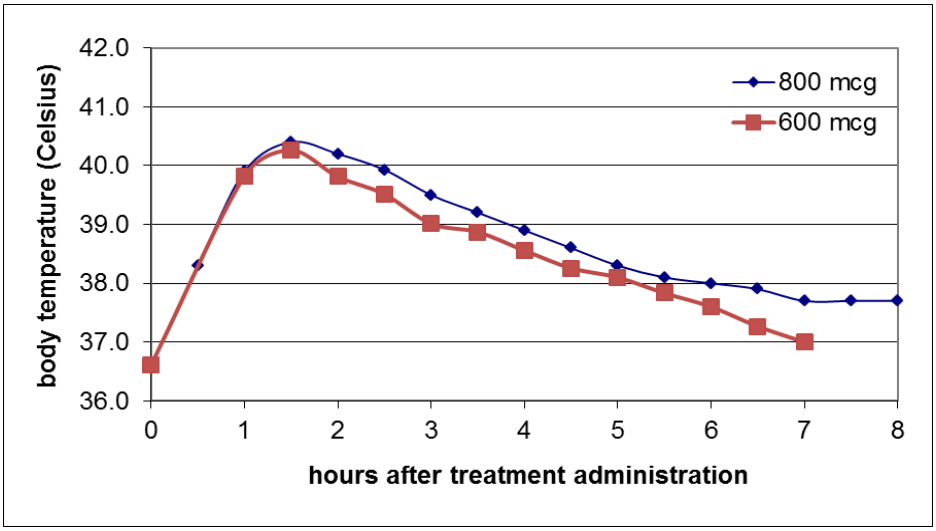
**This study enrolled Ecuadorian women exposed to uterotonics prophylactically and treated with 600 µg sublingual misoprostol for PPH (León 2012)*

*** These data are taken from another study that enrolled Ecuadorian women who were not exposed to uterotonics prophylactically and treated with 800 µg sublingual misoprostol. (These data were collected as part of a multi-country RCT (Winikoff et al 2010, country-level data not shown in publication)*

☼ *Other side effects: headache*

☼☼ *Other side effects: delirium/altered sensorium (10), headache (2), thirst (3), pain/cramping (3), excessive sweating (1), feel cold / teeth chattering (1)*

Figure 2 Average temperature trends for cases with high fever following 600 µg (n=8) and 800µg (n=58) doses of misoprostol for PPH treatment (León et al 2012)



11.2 Misoprostol and breastfeeding

Small amounts of misoprostol or its active metabolite have been found in breast milk; however, no adverse effects on nursing infants have been reported. The WHO's report titled the "Safety Profile of Misoprostol for Obstetrical Indications" reviews pharmacokinetic data from studies by Vogel et al (2004) and Abdel-Aleem et al (2003) and indicates that misoprostol levels in breast milk after a single oral dose rises and declines rapidly in nursing women which significantly lowers infant exposure. A study comparing misoprostol vs. methylergometrine on levels of excretion in breast milk confirmed that misoprostol has a shorter elimination half-life (1.1 vs. 2.3 hours) and 1/3 of the milk/plasma ratio, compared to methylergometrine (Vogel 2004; Bohlmann 2014).

For a nursing mother ingesting 200 µg oral misoprostol and producing 30 mL of breast milk, the maximum amount of misoprostol delivered in the milk is 109 pg, representing approximately 3 X 10^5 mg/kg in a 3.5kg newborn (1/100 that in the mother). The concentration of misoprostol in breast milk is likely insufficient to cause side effects in the breast-fed infant (Wannmacher 2010; EMA 2014). Indeed, a large community level trial among delivering women confirmed that after exposure to 600 µg oral misoprostol, breastfeeding did not cause any symptoms in the baby (Derman 2006). Based on current clinical and pharmacokinetic data, misoprostol does not have any breastfeeding contraindication.

11.3 Misoprostol and maternal mortality

To date, there is no evidence that misoprostol increases or reduces the risk of mortality (Hofmeyr 2013). Misoprostol's physiological effect on controlling blood loss has been well-documented, yet no studies have been large enough to confirm its effect on maternal deaths. A recent Cochrane review (2013) was completed to assess the relationship between postpartum use of misoprostol and maternal deaths, as well as determine its association with severe morbidity and pyrexia (Hofmeyr 2013). The review included all randomized trials of misoprostol for PPH prevention and treatment in order to achieve a large enough sample with adequate power. In total, 78 studies (59,216 women) were included: 71 prevention trials and 7 treatment studies. In

their analysis of maternal deaths, there was no statistical difference found when comparing studies of misoprostol versus all control groups, including placebo/no treatment or other uterotonics (31 studies; misoprostol 11/19,715 vs. control 4/20,076 deaths, risk ratio 2.08, 95% CI 0.82 to 5.28). Not all reported deaths were attributable to hemorrhage. The reviewers note that the overall number of maternal deaths in this review was too small for a meaningful statistical analysis.

Since publication of the 2013 Cochrane review, two community-based RCTs of 800 μg 800μg sublingual misoprostol for treatment of postpartum bleeding have been completed. In one study conducted in rural Egypt among home-births attended by midwives or nurse-midwives, 82 women were diagnosed with PPH and then randomized to receive either misoprostol or placebo for treatment of primary PPH. Two maternal deaths occurred in the placebo arm (2/48), compared to none in the misoprostol arm (0/34, p=0.509) (Hassanein, ICM 2014). In a recently completed cluster trial conducted in India, auxiliary nurse midwives were randomized to provide universal prophylaxis (administration of 600 μg oral misoprostol to all women) or secondary prevention (administration of 800 μg sublingual misoprostol only to women with >= 350 ml postpartum blood loss) for home-births and births at health sub-centres in rural India. In this study, no deaths occurred in either study arm (N=3032) (Goudar, SAFOG 2014).

Given the difficulty of measuring the effect of misoprostol (or any uterotonic) on maternal mortality, due the very large sample size (and # of events) that would be required, researchers have used mortality modeling to estimate its potential impact. Early studies have demonstrated with mathematical modeling that interventions with increased access to uterotonics and expanded community distribution of misoprostol can reduce maternal mortality by approximately a third (Pagel 2009; Sutherland 2009). A study by Prata (2014) in Bangladesh further substantiates these findings using Monte Carlo simulation techniques; increased coverage of misoprostol led to a greater reduction in maternal mortality. Sutherland et al. (2010) built upon previous findings modifying the Stochastic Simulator of Hemorrhagic Shock (SSHS) model, to address the impact of a misoprostol treatment package. They determined that misoprostol for treatment saves 9.4 lives per 10,000 women delivering at home relative to standard management, a delivery attended by a village health worker without access to medication.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

12.1 Range of Costs for the Proposed Medicine

The International Drug Price Indicator Guide 2013 published by Management Sciences for Health (MSH), was used to obtain present prices of misoprostol. The median supplier price listed was USD 0.3094 per 200μg tablet of misoprostol (USD 1.24 per dose for treatment). The median price paid by the three buyers listed was USD 0.12 per tablet (range USD 0.1-0.458); or USD 0.48 per dose for PPH treatment. Table 17 shows supplier price in USD and Table 18 shows buyer costs as listed in the report. A survey on the annual sales and manufacturer prices for 200-ug misoprostol found 85 registered products available worldwide. Based on this analysis and market trends, the authors concluded that misoprostol access is improving in low-income regions where it could have a significant impact on maternal mortality and morbidity (Fernandez MM et al, 2009). In May 2010, misoprostol became eligible for the WHO's Prequalification of

Medicines Programme; efforts are now underway to support applications from generic manufacturers of misoprostol. As misoprostol products achieve pre-qualification in the future, product availability may increase, and the unit price could drop making the drug even more cost effective.

Table 13 Supplier price information (USD) for 200 µg misoprostol tablets

Source	Package	Package Price	Unit Price
MEDS	30 Tab-cap	$5.89	0.1965/tab-cap
MSD/TANZ	20 Tab-cap (Tablets)	$4.80	0.2400/tab-cap
JMS	10 Tab-cap (Tablets)	$3.09	0.3094/tab-cap
MEDEOR/TZ	28 Tab-cap (Tablets)	$12.09	0.4318/tab-cap
UNFPA	60 Tab-cap (Blister-pack tablets)	$30.49	0.5081/tab-cap
Median Unit Price	**Lowest Unit Price**	**Highest Unit Price**	**High/Low Ratio**
0.3094/tab-cap	0.1965/tab-cap	0.5081 Highest Price	2.59

Table 14 Buyer price information (USD) for 200 µg misoprostol tablets

Buyer	Package Price (100 tablets)	Unit Price (USD)	Price per Dose (4 Tablets; 800µg)*
Organization of Eastern Caribbean States Pharmaceutical Procurement Service (OECS/PPS) 100 Tab-cap (Tablets)	$10.00	0.1000	0.4000
BDS 100 Tab-cap (Tablets)	$11.92	0.1192	0.4768
SAFRICA 60 Tab-cap (Tablets)	$27.48	0.4580	1.8320
Median Unit Price	**Lowest Unit Price**	**Highest Unit Price**	**High/Low Ratio**
0.1192	0.1000	0.4580	4.58

12.2 Comparative Cost-Effectiveness

In comparison to misoprostol, oxytocin has higher administration costs because it requires needles, syringes and tools to ensure safe injection, disposal and infection prevention practices. Unlike misoprostol, which can be stored at room temperature, oxytocin requires protection from light and temperature-controlled storage to prevent loss of potency, which may add to the overall cost burden. Some formulations of ergometrine have similar administration and storage costs.

Such requirements make oxytocin and ergometrine inaccessible/unavailable in limited resource settings, leaving misoprostol as the only intervention that can be offered. In such circumstances, misoprostol may be the only treatment option available. When this is the case, utilizing misoprostol to treat PPH may be more cost-effective than referral to higher level care with its associated costs. Bradley et al. (2007) found in their cost-effectiveness study of misoprostol to control PPH in low-resource settings that training traditional birth attendants (TBAs) to recognize postpartum hemorrhage and administer misoprostol would save approximately $115,000 in transport, hospital fees, IV therapy, and blood transfusions. Overall, the misoprostol strategy was deemed more cost-effective than the standard approach of TBAs referring women with PPH to hospitals (Bradley 2007). Side effects associated with use of misoprostol are

transient and rarely require additional treatments. Regardless any treatments required to treat fever are estimated to have minimal additional cost.

In one study that compared the cost-effectiveness of misoprostol for PPH treatment to other treatment methods, the authors assessed the net costs, cost-effectiveness, cost-benefit ratios and net benefits for preventative and curative interventions for PPH in four countries (Argentina, Bangladesh, India, and Nepal). In their analysis, the authors showed that there was considerable variation in the cost per Disability-Adjusted Life Year (DALY) averted due to the diversity of drug prices, labor and delivery patterns, and assumed coverage of each intervention in the four study countries (Seligman 2006). In an article by Sutherland et al. (2010), a Monte Carlo simulation was implemented to depict mortality and anemia-related morbidity due to PPH and expand upon previous cost-effectiveness analyses demonstrating the economic benefits of misoprostol distribution for the prevention of PPH (Sutherland 2010). They conducted a cost-evaluation comparing three community-based strategies in rural India: standard management; standard management plus 800 μg of sublingual misoprostol for PPH treatment; and standard management plus 600 μg of prophylactic oral misoprostol. The model accounted for the cost of the drugs, birth attendant training, and transport for women who did not respond to misoprostol. Authors found that use of misoprostol for treatment lowered mortality by 70% as compared to standard management. While adding misoprostol for treatment to standard management raised costs by 6%, it saved an estimated incremental cost of $6 per DALY. Further, when compared to a universal prophylaxis approach, a treatment strategy was found to be more effective (Sutherland 2010).

All of the interventions seeking to address PPH have a positive return. For now, misoprostol is perhaps the most cost-effective uterotonic to offer in low resource settings. In these contexts, community treatment models including advanced distribution of misoprostol and administration by lower level cadres of providers are suggested to be more cost-effective and impactful than the current standard of care with referral.

13. Summary of regulatory status of the medicine

Many formulations of misoprostol are available (See Appendix 1). Misoprostol was originally approved in the United States, where it was marketed and distributed as Cytotec® by Searle (now Pfizer) for prevention of gastric ulcers. Today, Cytotec® is registered in more than 80 countries for prevention gastric ulcers.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medical Agency approved Hemoprostol® for the treatment of PPH due to uterine atony. Marketed and distributed by Linepharma, France, Hemoprostol was approved under Article 58, which allows European pharmaceutical companies to market high quality medicinal products outside of the European Union, even when there is no authorization to do so in Europe.

The registration status of misoprostol varies from each country. Misoprostol products are registered for obstetric indications in more than 20 countries, including, Bangladesh, Bolivia, Cambodia, Ethiopia, France, India, Kenya, Malawi, Mali, Mozambique, Myanmar, Nepal, Pakistan, Senegal, Somaliland, Sudan, Tanzania, Uganda, Vietnam, and Zambia. The approved indications vary across countries; in some countries, products are only registered for PPH prevention and treatment, while in others they are registered for multiple obstetric indications.

Additionally, misoprostol may be legally used off label for obstetric indications in several countries (Misoprostol product brief: Reproductive Supplies Coalition).

Further, in May 2010, misoprostol became eligible for the WHO's Prequalification of Medicines Programme.

14. Availability of pharmacopoeial standards

Misoprostol (standards available in BAN, USAN, rINN)

15. Proposed text that could be included in a revised WHO Model Formulary

SECTION: 22.01.00.00 Oxytocics

FORMULATION (dosage form and strength): Oral tablet: 200 micrograms
ATC Code: A02BB01
Type of List: Core List

DISEASE/INDICATION: Treatment of postpartum hemorrhage.

RATIONALE FOR INCLUSION: Misoprostol is an effective, low-cost, easy to administer option to treat postpartum hemorrhage, one of the major contributors to maternal morbidity and mortality worldwide.

GENERAL INFORMATION: Misoprostol (600 μg) is included in the EML for prevention of PPH. It is also a complementary drug (with mifepristone) for medical termination of pregnancy of up to 63 days gestation, for management of incomplete abortion/miscarriage in women with uterine size ≤ 12 weeks gestational age, and for induction of labour.

USES: Treatment of postpartum hemorrhage due to uterine atony where intravenous oxytocin is not available.

CONTRAINDICATIONS (for use in PPH treatment): Known allergy to misoprostol.

DOSE: Treatment of postpartum hemorrhage, *sublingual administration (under the tongue)*,

ADULT and **ADOLESCENT** a single dose of 800 micrograms

NOTE: None

ADMINISTRATION: For treatment of postpartum hemorrhage, sublingual administration of four 200-microgram tablets (800 micrograms total) is recommended.

ADVERSE EFFECTS: shivering, fever.

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17. Appendix A – Partial List of Misoprostol (200 µg tablet formulation) Trade Names

Product name	Company
Aboprost	Cure Quick Pharmaceuticals, India
Alsoben	Unimed, South Korea, Unimed Pharm, Vietnam
Cedate-F	Profic Organic Ltd, India
Citrosol	PT. Otto Pharmaceutical Industries, Indonesia
Cyprostol	Pfizer, Austria
Cyrux	Serral, Mexico
Cystol	Korea United Pharm, South Korea
Cytil	Tecnoquímicas, Colombia
Cytofine	Master Farma, Peru
Cytolog	Zydus Cadila, India
Cytomis	Incepta Pharma, Bangladesh
Cytotec	Kaken Seiyaku, Japan
Cytotec	Pfizer , USA
Cytotec	Aliraif Searle, Turkey
Gastotec	JRP, South Korea
Gastrul	Fahrenheit, Indonesia
G-Misoprostol	Gonoshasthaya Pharmaceuticals, Dhaka, Bangladesh
Gymiso	HRA Pharma, France
Gymiso	MS Health Pty Ltd, Australia
Hemoprostol	Laboratorios León Farma, Spain
Industol	Laboratorio Franco Colombiano, Colombia
Isovent	Square Pharmaceuticals, Dhaka, Bangladesh
Kontrac	Fourts India, India
Mesopil	Nicholas Piramal, India
Mirolut	MIR Pharma, Russia
Misel	Shin Poong, South Korea
MISO	Bestochem, India
Misoclear	Zafa Pharmaceuticals, Pakistan
Misofar	Bial Industrial Farmaceutica, Spain
Misoplus	Walse Korea, South Korea
Misoprolen	Intipharm, Peru
Misopros V	Grupo Farmaceutico Colombiano, Colombia
Misoprost	Cipla, India
Misoprostol	Shanghai New Hualian Pharmaceutical Co., China
Misoprostol	Zizhu Pharmaceutical, China
Misoprostol	Servimedic, Uruguay
Misoprostol	Pentcroft Pharma, Russia
Misostad	Stada, Vietnam
Misotac	Sigma Pharm, Egypt
Misotrax	Otsira Genetica, India
Misotrol	Sanofi Aventis, Chile
Mizolast	Spectra (FDC Ltd), India

Noprostol	Novell Pharm, Indonesia
Ori-Prost	Orison Pharmaceuticals, India
Prestakind	Mankind, India
Prostokos	Hebron Pharma, Brazil
S.T. Mom	Zafa Pharmaceuticals, Pakistan
Tector	Zee Lab, India
U-Miso	U-Liang, Taiwan
Zitotec	Sun Pharma, India