17th 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:

Gynuity Health Projects, NY, USA

Jennifer Blum, MPH

Senior Program Associate

Gynuity Health Projects

15 East 26th Street, Suite 801

New York, NY 10010

Tel: (1) 212-448-1230

Fax: (1) 212-448-1260

jblum@gynuity.org

Yael Swica, MD, MPH

Senior Medical Associate

Gynuity Health Projects

15 East 26th Street, Suite 801

New York, NY 10010

Tel: (1) 212-448-1230

Fax: (1) 212-448-1260

yswica@gynuity.org

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1. Summary statement of the proposal for inclusion

Based on the currently available evidence, which includes several guidelines and numerous randomized and comparative clinical trials on the use of misoprostol for treatment of incomplete abortion and miscarriage, we propose that misoprostol be listed as a treatment for incomplete abortion and miscarriage on the World Health Organization's Model List of Essential Medicines. Of note, misoprostol is already included in the 14th and 15th editions of **WHO EML (22.1 Oxytocic)** because of its proven safety and efficacy for medical abortion and labor induction.

Misoprostol treatment for incomplete abortion could revolutionize care for the estimated 15% of women who experience miscarriage worldwide and ultimately contribute to a reduction in maternal morbidity and mortalities associated with poorly given surgical evacuations. Providers in many countries already use the drug for uterine evacuation as part of their standard practice; and listing its use for incomplete abortion on the WHO Model List of Essential Medicines would increase access to misoprostol into low-resource settings where it is probably most beneficial to women and providers. Misoprostol treatment for incomplete abortion would be particularly useful in places where standard surgical procedures, such as dilatation and curettage (D & C) and manual vacuum aspiration (MVA) are either not available and/or feasible. While each method comes with its pros and cons, choice of evacuation technique is ultimately a matter of trade-offs: MVA may be more effective, but it requires skilled providers with surgical skills, sterile instruments and equipped facilities. Surgical evacuation also carries risks for uterine perforation, cervical trauma, and infection. Misoprostol, on the other hand, may be slightly less effective and the evacuation may take longer, but it is less costly for the health system, and more easily accessible to women living far from highly equipped health facilities and skilled providers. The authors of a Cochrane review comparing surgical and expectant management make explicit this potential role for misoprostol treatment by stating that medical management gives another option to women with miscarriage who, until the introduction of misoprostol for this purpose, have had to "choose between an operation and doing nothing."[1]

This proposal is based on the following evidence and considerations:

1. Incomplete abortion contributes disproportionately to maternal morbidity and mortality in much of the developing world.

2. Misoprostol is effective. More than a dozen randomized or comparative trials showed that misoprostol has a success rate of 71-100% for treatment of incomplete abortion and miscarriage (See Table 1).

3. Misoprostol is safe. More than 600 studies have been published on the use of misoprostol in obstetrics and gynecology that have involved well over 90,000 women.

4. Medical evacuation of the uterus with misoprostol offers an alternative to surgical treatment, which in low-resource settings is often either unavailable or is associated with significant morbidity.

5. Misoprostol is inexpensive, and so offers a low-cost, but safe and effective means of treating this prevalent obstetrical condition.

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

Dr Catherine d'Arcangues, RHR Department

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

Gynuity Health Projects

4. International nonproprietary name of the medicine

Misoprostol

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

200 microgram oral tablet
100 microgram oral tablets

6. International availability - sources, if possible manufacturers

Misoprostol is widely available throughout the world, and has been available in generic formulation for several years. The first patent was granted in the United States, to Searle (now Pfizer), for marketing of Cytotec®, which continues to be the most widely distributed misoprostol tablet. Misoprostol has been off-patent in the United States for several years. As shown in Appendix 1, more than two dozen misoprostol products are currently marketed around the world. This list is not exhaustive and new products become available regularly.

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 in the 14th and 15th editions of **WHO Model List of Essential Medicines (22.1 Oxytocic)** because of its proven safety and efficacy for medical abortion and labor induction.

8. Information supporting the public health relevance

8.1 Disease burden

Early pregnancy failure is among the most commonly experienced medical conditions in the world. Up to 15% of recognized pregnancies miscarry, and as many as one in four women will experience a miscarriage at some point in her lifetime.[1] There also are approximately 46 million induced abortions worldwide each year, a proportion of which will be incomplete.[2]

Additionally, "unsafe" abortions are associated with high morbidity and mortality, in large part because a significant proportion are incomplete.[3] Unsafe abortion leads to an estimated 67,900 maternal deaths per year, with many times that number of women experiencing serious morbidity.[4] This is because unsafe abortions most commonly occur where abortion laws are restrictive or in places where lack of resources lead women to self-induce or seek services from less skilled professionals. Unsafe abortion occurs disproportionately in low resource countries, and constitute a major public health problem.

8.2 Treatment of incomplete abortion

Some studies have indicated that expectant management is effective in most cases of incomplete abortion.[5-7] Expectant management is a "watch and wait" approach. However, the appeal of expectant management may be diminished in low-resource settings, where women presenting with pain and bleeding at medical facilities may live far away with no access to reliable transportation. For such women and the facilities that serve them a requirement to remain at the hospital for observation can be both inconvenient and costly. Moreover, in all settings women are usually anxious to complete the abortion process in a predictable and timely manner so that they can get past this often physically and psychologically difficult experience.

Misoprostol treatment offers women and providers a highly acceptable alternative to both surgical and expectant management. Studies show that women prefer it to invasive surgery, and show that women with incomplete abortions choose medical treatment with misoprostol over surgery for that reason.[8-10] For these reasons, this method is slowly gaining attention as an easy to use, feasible, low-cost means of uterine evacuation that could revolutionize treatment for this condition.[11]

Many studies have shown that the uterotonic and cervical ripening properties of the prostaglandin E1 analogue misoprostol make it a safe and highly effective method of evacuating the uterus in cases of incomplete abortion[10, 12-14]. The stability of misoprostol at room temperature and its low cost make it an ideal treatment in low-resource settings. This simple to use method has the potential to improve greatly women's access to appropriate and effective care at secondary and even primary health care facilities which are often staffed with non-surgically trained providers. The potential benefits for healthcare provision in over-stretched low resource settings are enormous. Misoprostol for incomplete abortion has the potential to decrease the burden on tertiary healthcare centers, and reduce the costs for healthcare systems. The method could reduce the burden of care places on skilled surgical providers and reduce the need for surgical equipment and space. Finally, recent data show that misoprostol combined with a vaginal exam to detect an open cervical os can replace more costly treatment approaches that involve ultrasound, anesthesia, and surgical evacuation.[15]

8.3 Assessment of current use

In the United States, the use of misoprostol for treatment of incomplete abortion is now standard clinical practice for many providers. Interest in use of misoprostol for treatment of incomplete abortion is large and spawned, in part, a large NIH-funded study that assessed misoprostol vs. surgical management of early pregnancy failure to better inform providers as to appropriate regimens for medical management of incomplete (and also missed) abortions.[14]

Many European practitioners report that they also use misoprostol to manage incomplete abortions. Providers in low-resource countries have also begun to learn of the drug's usefulness for incomplete abortion and have begun to use it for this indication. A host of countries are now primed to add misoprostol management to country-level health care norms and regulations. Foremost among these is Madagascar, whose Ministry of Health approved use of 400 mcg sublingual misoprostol for treatment of incomplete abortion in 2006 (Diop A, *personal communication*, 2008). Many other countries would like to introduce misoprostol

for incomplete abortion care and would benefit from EML listing of the drug for this indication.

8.4 Target population

In low-resource settings, where few primary health care centers are equipped with ultrasound, early embryonic death is rarely diagnosed.[16] Instead, most women present with incomplete abortion, e.g., an open cervical os withy vaginal bleeding and/or incomplete passage of products of conception. Both spontaneous and induced abortions (it is often clinically difficult or impossible to distinguish between these) lead women to seek care for this condition. Women experiencing incomplete abortion make up a large part of the obstetric patient load in many low resource settings, accounting for 39% of all gynecological admissions in one large regional hospital in Tanzania.[10] Finding safe, effective, acceptable, and affordable means of treating incomplete abortion is therefore a priority, particularly for clinics and hospitals in low-resource settings.

Until recently, the only available treatment for incomplete abortion was surgery (dilatation and curettage [D&C]), which was then replaced by the equally effective but cheaper and safer manual vacuum aspiration (MVA). Unfortunately, MVA is not always available in low-resource settings, because it requires special equipment and training for use. Furthermore, surgical methods generally have increased risks associated with instrumentation of the uterus: trauma, infection, cervical tears, uterine perforation, bleeding, and reactions to anesthesia, among others. In low resource settings the highest risk of infection with spontaneous abortion occurs as a result of uterine instrumentation rather than the failure to promptly evacuate the products of conception.[16]

In many low resource countries, women residing far from tertiary and secondary level health care facilities do not have access to a trained and equipped surgical provider. This makes referrals, which are often costly and logistically burdensome, the only available treatment option. The misoprostol method of uterine evacuation could fill this service delivery gap by increasing the potential pool of providers available to treat this condition.

9. Treatment details

9.1 Dosage regimen[11, 17, 18]

A **single dose of 600 micrograms of oral misoprostol** is indicated for treatment of incomplete abortion for women who present with a uterine size less than or equal to 12 weeks gestation at time of treatment. This dose has successfully evacuated the uterus in over 1000 women in over a half a dozen trials worldwide.[9, 10, 19, 20, 11]

Recently completed trials testing 400 mcg sublingual misoprostol compared to 600 mcg oral misoprostol found that that the **400 micrograms sublingual dose** is as effective as 600 micrograms oral misoprostol when used for treatment of incomplete abortion.[22] Although the data in support of the 400 microgram sublingual misoprostol dose are less extensive, it may be shown in the future to be the optimal dose and route of administration for this indication.

9.2 Course and duration of treatment[11, 17, 18]

The course of treatment is brief and involves one to two outpatient visits. At the first visit, the incomplete abortion status should be confirmed by history and clinical exam, and eligibility for misoprostol should be assessed. Eligible women should have an open cervical os and a uterine size 12 weeks gestation or less. The expulsion process is usually not immediate, but occurs over several hours to several days. Typically women experience heavy bleeding for 3 to 4 days, followed by light bleeding or spotting for several weeks. Bleeding usually ends before the next menstrual period. Follow-up assessment is recommended 7 to 14 days following treatment. Surgical intervention is not recommended prior to 7 days after treatment unless doing so is medically necessary (i.e., for hemorrhage or infection control).

9.3 Need for special diagnostic or treatment facilities and skills[11, 17, 18]

Specialized diagnostic or treatment facilities are generally not needed as the method will work for most women. Nonetheless, providers and/or health care centers offering the misoprostol method should have referral networks set up with higher level facilities and/or providers who are equipped to manage complications. Complications that may require referral include undiagnosed ectopic pregnancy, heavy, ongoing bleeding and retained products of conception that may not evacuate on their own. In the absence of complications requiring higher level care, clinically stable women presenting with retained products at follow up can also be offered another dose of misoprostol.[12, 13]

Clinical assessment alone should enable a provider to determine the need for surgical intervention; although occasionally ultrasound confirmation will be needed. Medical facilities offering back up care services should thus have access to ultrasound. Most of the initial trials on misoprostol for incomplete abortion were conducted in high resource settings and thus were highly dependent on ultrasound as a diagnostic tool. Later trials in low resource settings used the technology less frequently. For instance, in a trial conducted in Moldova and Madagascar, ultrasound use was limited, with follow up assessed by ultrasound in fewer than 3% of cases in Madagascar and roughly 30% of the time in Moldova.[22] A review of data collected in five low resource settings revealed that ultrasound was used as a diagnostic tool at patient intake in approximately 30% of cases. In these same studies, the technology was used to confirm abortion status in less than 5% of cases (Blum J, *unpublished*

analysis. 2008). Safety and efficacy rates in all of these studies were high, showing that the method can be safely administered to women in the absence of ultrasound confirmation.

Routine antibiotic coverage is not necessary and local norms regarding antibiotic use for treatment of incomplete abortion should be followed (see section 11.3). A Cochrane review assessing the value of routine antibiotics before surgical evacuation (but not misoprostol management) of incomplete abortion found that there is insufficient evidence to evaluate routine antibiotic coverage.[23] Clinical exam and patient history remain reliable ways for providers to determine the need for antibiotic coverage based on history or clinical exam.

9.4 Published guidelines on the use of misoprostol for incomplete abortion

Blum J, Winikoff, Gemzell-Danielsson K, Ho PC, Schiavon R, Weeks A. Treatment of incomplete abortion and miscarriage with misoprostol. *International Journal of Obstetrics and Gynecology* (2007) 99, S186-S189.

RCOG Guideline No. 25: The Management of Early Pregnancy Loss. Royal College of Obstetricians and Gynaecologists: London, U.K. (2006).

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

10.1 Identification of clinical evidence

We understand that a Cochrane Review of misoprostol for treatment of incomplete abortion is pending, and therefore its results could not be included in this application. Table 1 lists all published trials for misoprostol treatment of incomplete abortion/miscarriage. This review was done by searching via PubMed for all trials published in the English language through September 2008. When possible, trials published in other languages were reviewed.

10.2 Summary of available data

10.2a Dose finding

The 600 microgram dose and oral route of misoprostol administration proposed in this application were identified on the basis of dose finding studies comparing a single 600 mcg oral dose of misoprostol to a repeated dose regimen (600 mcg X 2, Q 4) among 469 women in Thailand and Vietnam.[12, 41] In these studies, ultrasound was systematically used at entry and exit to confirm abortion status. The results slightly favored a repeat dose in Thailand: 87% versus 82% (with one dose).[12] In Vietnam, where the sample size was twice that of Thailand, there was no difference in efficacy between the two regimens: 95% for the single dose and 94% for the repeated dose.[41] Consequently, in an effort to identify the lowest effective treatment dose that also hewed to budgetary and service delivery considerations, researchers concluded that the single dose regimen was best suited to future use and investigation.

A recent study in Moldova and Madagascar compared 600 mcg oral misoprostol to 400 mcg sublingual misoprostol among 300 women treated for incomplete abortion showed no difference in efficacy for the two regimens: 94.6% with 600 mcg orally and 94.5% with 400 mcg sublingual groups (p=0.98).[22] These data suggest that misoprostol is effective regardless of whether administered orally (600 mcg) or sublingually (400 mcg). Several large, at yet,

unpublished studies of the 400 mcg sublingual regimen have been presented at recent scientific meetings. In total, these data include an additional 600 women successfully treated for incomplete abortion with this lower dose regimen.[24]

10.2b Reports of efficacy from studies comparing misoprostol to standard surgical care

In published studies, success ranges between 13% and 100%, with a median of approximately 92%, and 13 out of 22 studies reporting rates of 90% or better. [5, 9, 10, 12,14, 19, 20, 25-38,41] (Table 1) The success rate reported in trials is closely related to the length of time after treatment at which the uterus is reassessed by ultrasound exam.[16] Early studies on the use misoprostol for incomplete abortion tested a range of doses (400 mcg to 1200 mcg) and routes (oral, vaginal, intrauterine, etc.), and showed variable rates of effectiveness (13-66%).[27-29, 36] Careful interpretation of these results is complicated by the fact that the dosing regimens tested vary greatly, as do, in most cases, the clinical definitions for "success". Often, the assessments of outcome were confounded by premature clinical evaluations, which were in many trials done within the first day of treatment. For example, Chung et al. in a prospective, observational study of 225 women with incomplete or spontaneous abortion treated with repeated doses of 400 mcg oral misoprostol, assessed clinical outcome with transvaginal ultrasound 48 hours after misoprostol initiation.[27] The short interval between treatment outcome and clinical assessment may have contributed in part to the relatively low success rate of 66%.

Evidence from these studies was, however, convincing enough to encourage researchers to undertake more careful studies, with strict entry and exit criteria upon which to generate reliable data on the drug's efficacy for incomplete abortion care. Most of these trials were conducted in low resource setting hospitals with limited facilities, and thus also provide some external validity as to how the method might be operationalized in such settings. In these trials, a 600 mcg oral dose was tested in more than 1000 women.[9, 10, 19, 20] In most cases, complete uterine evacuation was ascertained using clinical criteria alone. Only one of four published studies (in Burkina Faso) testing this regimen required that women have their abortion status validated by ultrasound. In all other locations (Tanzania, Mozambique, Uganda), ultrasound was available for use if considered necessary to determine the woman's abortion status.

According to guidelines set forth by the Royal College of Obstetricians and Gynecologists (RCOG) for rating quality of evidence, the 600 microgram oral dose has a strong evidence base.[18] The evidence base for the 400 microgram sublingual misoprostol regimen is weaker; however it is expected to be equally strong once in press and completed trials are published.

10.2c Satisfaction and acceptability of misoprostol treatment

Data show that misoprostol is highly acceptable to women for treatment of incomplete abortion. For example, in one study of 447 women in Burkina Faso, the majority of women reported that they were "satisfied" or "very satisfied" with the method they received (misoprostol=96.8%, MVA=86.6%), would choose that method again (misoprostol=94.5%, MVA=86.6%) and would recommend it to a friend (misoprostol=94.5%, MVA=85.2%).[19]

Other randomized trials show that women find misoprostol to be more acceptable than MVA for treatment of incomplete abortion. A trial enrolling 300 women in Tanzania found that more women were very satisfied with misoprostol (75%) than with MVA (55%) (p=0.001), and a higher proportion of women in the misoprostol arm said that they would recommend

the treatment to a friend (95% versus 75%, p<0.001).[10] This sentiment was echoed in another trial of 270 women in Mozambique; those who were allocated to misoprostol were significantly more likely to be "very satisfied" with the treatment and willing to choose the method again (misoprostol= 86.5%, MVA= 36.6%, p<0.001).[9]

A Hong Kong trial assessing psychological impact and client satisfaction with medical versus surgical treatment for spontaneous abortion found no difference in reported rate of satisfaction among women treated with misoprostol or surgery.[39] Women for whom misoprostol failed and therefore surgical back-up was needed were generally less satisfied than those for whom the given method succeeded. Misoprostol users were more likely to say that they would recommend the method to a friend: 79% versus 69% (p.0.05) and that they would choose the method again: 79% for misoprostol versus 48% for surgery (p.0.01).

Table 1. Misoprostol for treatment of incomplete abortion in the first trimester

Studies listed in **ascending** order of success rate.

(Shaded rows = Studies in which more than 50 women were treated with misoprostol)

Lead author [Ref.]	Miso dose (µg), route, & dosing schedule	n (misoprostol group)	Success rate (%)	Maximum time for definition of success (hours)	Comparison group (n; success rate)
De Jonge,1995[29]	400 oral	23	13	12 h	Surgery (27; 97%)
Chung, 1995[28]	400 oral q 4 max 3 doses	141	62	≤24 h	
Pang, 2001[36]	800 oral 800 vag (q 4 h max 2 doses)	105 96	64 61 (63¶)	≤24 h	
Blanchard, 2004[12]	600 oral 600 oral q 4 X 2 doses	82 87	66 70 (68¶)	14 days	
Chung, 1997[27]	1200 oral divided into 3 doses over 24 h, repeated a 2nd day, if necessary	225	66*	48 h	Surgery (137; 97%)
Trinder, 2006[5]	800 vag	90	71	8 h (?)	Surgery (92; 98%) EM (92; 75%)
Shelley, 2005[38]	400 vag repeated once at 4-6 h	10	80	10-14 days	Surgery (11; 100%) EM (14; 86%)
Pandian, 2001[35]	600 oral, then 400 oral q 2 max 2 doses	112	85	(several hours?)	
Blohm, 2005[26]	400 vag, 1 dose	64	88	> 14 days	Placebo (62; 60)
Gronlund, 2002[31]	400 vag	31	90	14 days	EM (17; 82%) Surgery (30; 97%)
Moodliar, 2005[33]	600 vag q 24 max 2 doses	47	92	8 days	Surgery (47; 100%)
Zhang, 2005[14]	800 vag q 48 max 2 doses	30	93	7 days	Surgery (148; 97%)‡
Demetroulis, 2001[30]	800 vag	14	93	8-10 h	Surgery (16; 100%)
Sahin, 2001[37]	200 vag, then 200 oral 4 times/day max 5 days	40	93	14 days (?)	Surgery (40; 100%)

Lead author [Ref.]	Miso dose (µg), route, & dosing schedule	n (misoprostol group)	Success rate (%)	Maximum time for definition of success (hours)	Comparison group (n; success rate)
Ngoc, 2004[41]	600 oral 600 oral q 4 X 2 doses (not max all got 2 doses)	150 150	95¶ 94	9 days	
Henshaw, 1993[32]	400 oral	24	95**	12-18 h	Sulprostone (20;**)
Weeks, 2005[20]	600 oral	160	96	Up to 14 days	Surgery (152; 92%)
Shwekerela, 2007[10]	600 oral	150	99	Up to 14 days	Surgery (150; 100%)
Ngai, 2001[34]	400 vag q 48 up to 3 doses	5	100	43 days	EM (10; 80%)
Bagratee, 2004[25]	600 vag q 24 up to 2 doses	7	100	6 days	Placebo (14; 86%)
Dao, 2007[19]	600 oral	223	94.5	7 days	Surgery (224; 99.1%)
Bique, 2007[9]	600 oral	123	91.0	7 days	Surgery (124; 100%)

Vag=vaginal; mife=mifepristone; EM=expectant management; "?" indicates that the given article is not clear on the given point.

* This study reports a 70% success rate, but careful reading of the text suggests that 66% is a more correct figure.

** Experimental and comparison groups combined b/c no difference in success.

‡ Includes cases of missed abortion. ¶ Weighted average.

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Misoprostol has been called "one of the most important medications in obstetrical practice".[40] It is a synthetic analogue of the biologic prostaglandin E1. Natural and synthetic prostaglandins are known to affect the female reproductive system. Misoprostol has been used very broadly for the past twenty five years in obstetrics: for induced abortion, miscarriage, labor induction, and prevention and treatment of post-partum hemorrhage. More than 600 studies have been published on the use of misoprostol in obstetrics and gynecology that have involved well over 90,000 women.

With respect to the use of misoprostol to treat incomplete abortion, more than 2,000 women have been exposed to the treatment, and more recent trials – with refined regimens and protocols built on past research and clinical experience – show remarkably high success with more than 9 out of ten women have successful uterine evacuations with misoprostol.

11.2 Side effects after misoprostol[11]

Prolonged or serious side effects of misoprostol used for incomplete abortion are rare. However, bleeding and cramping are expected effects that are related to the therapeutic process. Potential side effects of the drug include fever and/or chills, nausea and vomiting, diarrhea and skin rash. Bleeding is common and typically lasts up to two weeks with additional days of spotting that can continue until the next menstrual period. In five randomized controlled trials (n=1484) women reported significantly more "heavy" (more than a period) and "normal" (same as a period) bleeding with misoprostol than following MVA.[9, 10, 19, 20, 41] Women in both arms reported similar amounts of "light bleeding" (less than a period) or "spotting" following either MVA or misoprostol treatment.

Self-reporting of heavy bleeding by misoprostol users is to be expected. With MVA, the bulk of uterine bleeding occurs during the procedure itself, so only the clinician observes the heaviest bleeding. By contrast, misoprostol treatment either initiates or briefly intensifies bleeding (depending on clinical presentation), and the woman, not the provider, is the main observer of this therapeutic process. Most important, though, with respect to firm clinical endpoints, very few serious adverse events (including blood transfusion and anemia) were reported in any of the studies.

Other side effects of misoprostol include cramping, nausea, vomiting and diarrhea, fever and chills, most of which typically self-resolve within a few hours.[42] In studies that compared 600 mcg oral misoprostol to MVA for treatment of incomplete abortion, cramping was reported by 56 to 95 percent, nausea and vomiting by 5 to 33 percent, chills by 5 and 85 percent, fever by 0.4 to 2 percent, and fever/chills by 3.8 and 15% of women.[9, 10, 13, 19, 41] Cramping generally starts within the first few hours but may begin as early as 10 minutes after misoprostol administration. The pain may be stronger than that experienced during a regular period. Non-steroidal anti-inflammatory drugs (NSAIDS) or other analgesia can be used for pain relief without affecting the success of this method.[43] Nausea tends to resolve in 2 to 6 hours following misoprostol administration. Women can be advised to take an anti-emetic if needed. Diarrhea is not frequently recorded in the published studies. In one study that compared MVA to misoprostol, 51 percent of women who used misoprostol report diarrhea.[13] Chills are a common side effect of misoprostol but are transient and usually subside after 24 hours. Fever is less common and does not necessarily indicate infection. An antipyretic can be used for relief of fever, if needed. Very rarely, a mild skin rash occurs after administration of misoprostol. This effect has not been reported in the literature on misoprostol for treatment of incomplete abortion but has been reported in relation to the drug's use for medical abortion and as well as other indications.[42] If rash occurs, no intervention is needed but in the event of skin irritation, an antihistamine, such as Benadryl®, can be provided.

Data on side effects of oral versus sublingual regimens was collected in the Moldova-Madagascar study with no significant differences found between the two regimens. In this study, approximately two-thirds of women reported abdominal pain with no difference between groups: 62.6% oral and 67.3% sublingual. Similarly there was no difference in reports of bleeding - 24% and 26% in the oral and sublingual groups, respectively. Other side effects during the observation period were rare and included headaches (1%) and dizziness/weakness (1%).[22]

11.3 Infection and provision to women after suspected unsafe abortion

Some providers have expressed concerns about treating incomplete abortions with misoprostol among women who may have tried to self-induce with misoprostol before presenting at the health facility. There is no evidence showing that these women are not candidates for misoprostol treatment. In fact, given that the half-life of misoprostol is quite short, it is highly unlikely that an additional 400 mcg or 600 mcg dose of misoprostol will have an adverse effect. As mentioned above, several studies have tested repeated misoprostol doses for this indication and have found no harm in giving a second dose.[12, 13] There is also no evidence showing that the treatment will not work for women who are experiencing incomplete abortion after a misoprostol-induced abortion. In the extensive literature on mifepristone medical abortion, there is evidence that incomplete abortions can be resolved with another dose of misoprostol.

Further, in under-resourced settings unsafe abortion procedures place women at greatest risk of harm; regardless of whether or not the present abortion is induced or spontaneous. As outlined by Weeks in the WHO RHL, "in settings where there are high rates of HIV/AIDS, pelvic inflammatory disease, and cervical infection, one should try to avoid surgical instrumentation of the uterus with either manual vacuum aspiration or sharp curettage. The small risks of allowing the products of conception to remain within the uterus can be reduced by the use of misoprostol to empty the uterus".[16] Misoprostol treatment reduces the risk of infection associated with surgical terminations simply because it is a hand-off, no instrumentation procedure. As evidenced in the literature on medical abortion in early pregnancy, the risk of infection to the upper genital tract is low if no uterine instrumentation occurs.[44] A U.K. study comparing medical, surgical and expectant management also found no difference in the rate of infection at follow up day 10 – 14 among 1200 women allocated to one of these treatments: surgical=3%, expectant management=3% and medical=2% (RR; 95% CI for surgical versus medical 0.7; -1.6 to 3.1).[5]

Generally speaking, women presenting with signs of pelvic infection, severe systemic infection or sepsis may be better candidates for surgical evacuation; while women with signs of infection that are not clinically severe can be offered misoprostol. In both instances, antibiotic coverage and assessment for anemia, should be provided according to standard clinical practice to ensure best outcome.

11.4 Use among women with a previous cesarean section

There is no reason to withhold misoprostol for treatment of incomplete abortion in women with previous cesarean section. While many clinical trials have excluded women with previous cesarean section when testing misoprostol for other indications, studies on this indication have not excluded such women. (Note: uterine size of < 12 weeks will ensure that misoprostol remains safe for women with uterine scars.)

11.5 Use in women with advanced gestational age (beyond the 12 week gestational size recommended in this application)

Recommendations for specific regimens at advanced gestational ages or with uterine size > 12 weeks' LMP have not been put forth in this application.

11.6 Summary of safety against comparators

11.6a Misoprostol vs. expectant management (EM)

As shown on Table 1, six studies have compared misoprostol to expectant management, either explicitly or implicitly (by comparing misoprostol with placebo).[5, 25, 26, 31, 34, 38] Success rates for misoprostol range from 71-100% in these studies, compared with 60-86% for EM. No large studies have compared misoprostol to expectant management for treatment of incomplete abortion. One large, randomized controlled trial (n=1200) of miscarriage management, with expectant, medical and surgical arms found no significant differences in the incidence of infection or serious adverse events among the three methods.[5]

In low-resource settings where background infection rates are high and women may be immunocompromised, expectant management may be less safe than medical evacuation of the uterus.

11.6b Misoprostol vs. surgical completion (Dilation & Curettage [D & C] or Manual Vacuum Aspiration [MVA])

Thirteen studies compare treatment with misoprostol to surgical intervention, either D&C or MVA.[5, 9, 10, 14, 19, 20, 27, 29-31, 33, 37, 38] Median success of misoprostol and surgery was 92% and 98%, respectively. Four studies compared 600 mcg oral misoprostol to MVA for treatment of incomplete abortion.[9, 10, 19, 20] Weeks et al. (n=312) showed a success rate of 96.3% with misoprostol, which was slightly better than with MVA (91.5%).[20] As shown in Table 1, randomized trials in Tanzania, Burkina Faso and Mozambique has similar results, with efficacy for misoprostol ranging from 90% to 99% and efficacy for MVA ranging from 99.1% to 100%.[9, 10, 19]

These results show that misoprostol is a safe and effective alternative to surgery or expectant management. In fact, a 2006 Cochrane review comparing surgical management to EM found insufficient evidence to support a recommendation of either EM or surgical completion over the other.[1] Instead, the authors discuss the trade-offs of each treatment approach. They suggest that EM is an acceptable method for women who are not concerned about bleeding and willing to accept a higher rate of continued incomplete abortion (with possibly a later surgical evacuation). This is because EM has a lower risk of risk of infection compared to surgical management. Misoprostol fits well within this strategy; like EM, misoprostol completion may take longer, but it is unlikely to have as high a risk of infection as surgery. In a service delivery continuum, misoprostol falls somewhere between EM and surgical management. In fact, because of misoprostol, the Cochrane Review authors write, "women no longer have to choose between an operation and doing nothing." The misoprostol option therefore fills a therapeutic void in incomplete abortion care.

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

Misoprostol is inexpensive. According to the *International Drug Price Indicator Guide* (Table 12.1a), the median price per 200 microgram tablet is 0.22 US cents, with a range of 0.09 to 0.36 US cents.[47] The median price paid by the two buyers listed was USD 0.22 per tablet (range USD 0.09-0.36). The recommended dose for treatment of incomplete miscarriage is 600 micrograms, or 3 tablets. Therefore, the median price per woman treated

with a 600 microgram dose would be, 0.67 US cents, with a range of 0.27 US cents to 1.07 US dollars.

Table 12.1a Price information (in US$)			
Supplier Prices			
Source	Package	Package Price	Unit Price
ACTION/IH	28 Tab-cap (Tablets)	17.57	0.6274/Tab-cap
Buyer Prices			
OECS/PPS	100 Tab-cap (Tablets)	$ 9.00	0.0900 /Tab-cap
BDS	100 Tab-cap (Tablets)	$ 35.65	0.3565 /Tab-cap
Median Price	**Lowest Price**	**Highest Price**	**High/Low Ratio**
0.2233/Tab-cap	0.0900/Tab-cap	0.3565/Tab-cap	3.96

Source: International Drug Price Indicator Guide (Management Health Sciences, 2006)

A cost analysis conducted in the U.K., that compared medical management, surgical management and expectant management of incomplete or missed miscarriage, found that expectant and medical management were less expensive than surgical management (1,086.20 English pounds and 1,410.40 GBP, respectively, versus 1,585.30 English pounds for surgical management).[48] A similar study conducted in Hong Kong found that medical management was less costly ($1,000 US) than either surgical ($2,007 US) or expectant management ($1172 US).[49]

13. Summary of regulatory status of the medicine

Worldwide, several 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, which then became part of Pharmacia, which, in turn merged with Pfizer.

14. Availability of pharmacopoeial standards

Misoprostol (standards available in BAN, USAN, rINN)

15. Proposed (new/adapted) text for the WHO Model Formulary

We propose the following text for addition to the current WHO Model Formulary, under section 22.01.00.00, Oxytocics, Misoprostol.

Dosage form and strength: Oral tablet: 200 micrograms; **ATC Code**: A02BB01; **Type of List**: Complementary List.
Rationale for inclusion: Medical treatment of incomplete abortion is sometimes needed for uterine evacuation after failed pregnancy.

Indication: Treatment of incomplete abortion for women with uterine size less than or equal to 12 weeks LMP at presentation.

Contraindications: History of allergy to misoprostol or other prostaglandin; suspicion of ectopic pregnancy; signs of pelvic infection and/or sepsis; signs of hemodynamic instability or shock.

Precautions: Eligible women with an IUD/IUS in place should have the IUD/IUS removed before drug administration; caution is advised when treating women with known bleeding disorders or currently taking anti-coagulants; May be used in patients with uterine size greater than 12 week but with a known gestational age less than or equal to 12 weeks (e.g., where uterine enlargement is not due to pregnancy but to myomata, for example); Small amounts of misoprostol or its active metabolite may appear in breast milk. There are no known consequences of this and no reports of adverse events on nursing infants.

Interactions: None.

Dosage: Treatment of incomplete abortion, *oral administration*, **ADULT** and **ADOLESCENT,** a single oral dose of 600 micrograms is recommended. A single sublingual dose of 400 micrograms is also recommended (as data become more available).

Adverse effects: Prolonged or serious side effects are rare. After administration of misoprostol, bleeding typically lasts up to two weeks with additional days of spotting that can last until the next menstrual period. Cramping usually begins within the first few hours after administration, but can begin as soon as (10 or 30) minutes after misoprostol administration. The pain may be stronger than that experienced during a normal menstrual period. Chills, fever, nausea, vomiting, and diarrhea are common side effects, but occur transiently, subsiding within 24 hours.

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Appendix 1: Table of Partial List of Product Sources

Product name	Composition	Company
CYTOTEC tab	Misoprostol 200mcg	**PFIZER, USA**
CYTOTEC tab	Misoprostol 100mcg	**PFIZER, USA**
CYTOLOG tab	Misoprostol 200mcg	**ZYDUS, INDIA**
MESOPIL tab	Misoprostol 200mcg	**NICHOLAS, INDIA**
MESOWIS tab	Misoprostol 200mcg	**WISDOM, INDIA**
MISO tab	Misoprostol 200mcg	**BESTOCHEM, INDIA**
MISOPROST tab	Misoprostol 100mcg	**CIPLA, INDIA**
MISOPROST tab	Misoprostol 200mcg	**CIPLA, INDIA**
MISOTOL tab	Misoprostol 200mcg	**RESMED, INDIA**
PRESTAKIND tab	Misoprostol 200mcg	**MANKIND, INDIA**
TECTOR tab	Misoprostol 200mcg	**ZEE LAB, INDIA**
ZITOTEC tab	Misoprostol 100mcg	**SUN PHARMA, INDIA**
ZITOTEC tab	Misoprostol 200mcg	**SUN PHARMA, INDIA**
MISOPROSTOL tab	Misoprostol 100mcg	**IVAX, US**
MISOPROSTOL tab	Misoprostol 200mcg	**IVAX, US**
GYMISO tab	Misoprostol 200mcg	**HRA Pharma, France**
MISOPROSTOL tab	Misoprostol 200mcg	**Pentcoft Pharma, Russia**
U MISO tab	Misoprostol 200mcg	**U Liang Pharma, Taiwan**
MIROLUT tab	Misoprostol 200mcg	**Mir Pharma,Russia**
CYTOMIS tab	Misoprostol 200mcg	**Incepta, Bangladesh**
PROSTOKOS tab	Misoprostol 200mcg	**Hebron Pharmaceuticals, Brazil**
CYTIL tab	Misoprostol 200mcg	**Tecnoquímicas, Colombia**
MISOTAC tab	Misoprostol 200mcg	**Sigma Pharm, Egypt**
MISOSTAD tab	Misoprostol 200mcg	**Stada, Vietnam**
ALSOBEN tab	Misoprostol 200mcg	**UNIMED PHARM, Korea**