Application for inclusion of
mifepristone combined with misoprostol
for first trimester (until 9 weeks) medical abortion
in the WHO Model List of Essential Medicines

1. Summary statement of the proposal for inclusion
Mifepristone 200 milligram (mg) followed by misoprostol 800 microgram (mcg) (4 times 200 mcg) vaginally has been shown to be equally effective compared to surgical methods in terminating pregnancy until 9 weeks. Complications such as incomplete abortion and hemorrhage are rare. In countries where it has been licensed, an increasing number of women are choosing medical abortion. It is a safe, discrete and effective method that provides women a more natural way to terminate their pregnancy and should therefore be included in the WHO List of Essential Medicines.

2. Name of the focal point in WHO submitting application
Dr Helena von Hertzen, Medical Officer, UNDP/UNFPA/WHO/World Bank Special Programme for Research in Human Reproduction, Department of Reproductive Health and Research, Family and Community Health Cluster (WHO/RHR).

3. Name of the organization consulted and supporting the application
The Geneva Foundation for Medical Education and Research (GFMER; http://www.gfmer.ch/) is submitting the application. GFMER is a WHO Collaborating Centre in Education and Research in Human Reproduction. Staff at GFMER has extensive experience in conducting systematic reviews, critically appraising the literature and developing recommendations.

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

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group
Two individual medicines as a sequential regimen.

6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

   • Number of abortions worldwide:
In developed countries, of the 28 million pregnancies occurring every year, 36% end in abortion.
In developing countries, of the 182 million pregnancies occurring every year, 20% end in abortion. Almost 80% of all abortions are conducted in developing countries (1).
Worldwide, 3.6% of women aged 15-44 are estimated to have pregnancy terminations yearly, which make a total of more than 46 million abortions per year (1).

- **Problem of unsafe abortion:**
  According to WHO, 19 million women have an unsafe abortion worldwide each year and 18.5 million of these occur in developing countries (2) and mortality due to unsafe abortion is estimated about 68,000 women each year (3).
  Complications due to unsafe abortions can be: infections (sepsis), uterine perforation, cervical laceration, incomplete evacuation, hemorrhage, miscarriage, future sterility and death.
  In settings where termination of pregnancy is legal, it can still be unsafe when performed under inappropriate circumstances such as in an non-sterile environment with lack of proper equipment and emergency drugs, or by untrained personnel.
  Medical methods offer a safe treatment alternative in those settings where abortion is legal, but unsafe as the treatment administration requires little training and a simpler infrastructure compared to surgical procedures (4).

7. **Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)**

- **Dosage regimen:** sequential regimen mifepristone 200 mg orally/misoprostol 800 mcg (4 times 200 mcg) vaginally.
- **Duration:** Mifepristone is taken as a single dose followed by misoprostol 36 to 48 hours after as a single dose.
- **Diagnostic:** Diagnosis of pregnancy is required. Mifepristone followed by misoprostol is used to terminate pregnancy up to 9 weeks.
- **Treatment facilities:** Ultra-sound before and after medical abortion may be of benefit in the diagnosis of pregnancy and to confirm complete abortion.
  Women who underwent the treatment should be followed-up 10 to 15 days after termination to make sure that the treatment was effective and that no complications had occurred.
  In case of an incomplete or failed abortion, surgical abortion is required. Facilities providing medical treatment must provide surgical back-up, such as vacuum aspiration.

8. **Summary of comparative effectiveness in a variety of clinical settings:**

- **Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)**

Concerning search strategy, the Cochrane Controlled Trials Register, Medline and Popline were systematically searched. Reference lists of retrieved papers were also searched and experts in WHO/HRP were contacted.

A recently published Cochrane systematic review comparing the different medical methods for first trimester abortion for their effectiveness was identified (5):
Studies considered for the systematic review were randomized controlled trials comparing different medical methods (e.g. single drug, combination), ways of...
application, or different dose regimens, single or combined, for medical abortion. Trials were assessed and included if they had adequate concealment of allocation, randomization procedure and follow-up. Different medical methods for first trimester abortion compared with each other were included. Participants were pregnant women in the first trimester undergoing abortion.

Two reviewers independently selected the trials for inclusion from the results of the search strategy. Studies selected were evaluated for appropriateness for inclusion and methodological quality without consideration of their results.

The outcome measures were failure to achieve complete abortion, surgical evacuation (as emergency procedure, non-emergency-procedure, or undefined), ongoing pregnancy at follow-up, time until passing of conceptus (> 3-6 hours), blood transfusion, blood loss (measure or clinically relevant drop in hemoglobin), days of bleeding, pain resulting from the procedure (reported by the women or measured by use of analgesics), additional uterotoniccs used, women’s dissatisfaction with the procedure, nausea, vomiting, diarrhea.

Thirty-nine trials were included in the review. Results were reported as relative risk (RR) with 95% confidence interval (CI) for categorical data and as weighted mean difference (WMD) for continuous data.

Outcomes:
1) Combined regimen mifepristone/prostaglandin: mifepristone 200 mg compared to 600 mg shows similar effectiveness in achieving complete abortion (4 trials, RR 1.07, 95% CI 0.87 to 1.32).
2) Combined regimen mifepristone/misoprostol: misoprostol administered orally is less effective (more failures) than vaginally (2 trials, RR 4.41, 95% CI 2.32 to 8.38) and may be associated with more frequent side effects such as nausea and diarrhea.
3) Mifepristone alone is less effective compared to the combined regimen mifepristone/prostaglandin (3 trials, RR 3.76 95% CI 2.30 to 6.15).
4) Five trials were included in the comparison of prostaglandin alone compared to the combined regimen. All but one reported higher effectiveness with the combined regimen compared to prostaglandin alone. The results of these studies were not pooled because different combined regimens were used in the trials but the RR of failure with prostaglandin alone is between 1.4 to 3.75 times higher than with the combined regimen.

Concerning gestational age, studies have shown that the effectiveness of medical abortion decreased with gestational age (6). In this review, trials included women up to 9 weeks of pregnancy.

This submission does not refer to pregnancies beyond 9 weeks of pregnancy.

9. Summary of comparative evidence on safety:

- **Estimate of total patient exposure to date to medical abortion**
In about thirty countries where medical abortion has been registered millions of women have used it. It has been registered in France in 1989, in the United Kingdom in 1991 and in Sweden in 1992 followed by other European countries between 1999 – 2001.
• **Description of adverse effects/reactions**
The effects of medical methods for termination of pregnancy are similar to those associated with spontaneous abortion and include cramping and prolonged menstrual-like bleeding. Some side effects such as pain and nausea are due to pregnancy and can be alleviated by simple analgesics or antiemetics. Side effects related to drugs are very rare (7). An uncommon complication is continuing pregnancy (1 to 3% of cases). In the later case, surgical abortion is needed to complete the abortion.

• **Identification of variation in safety due to health systems and patient factors**
Contra-indications for the use of mifepristone/misoprostol are allergies to one of the substances, ectopic pregnancy, chronic or acute adrenal or hepatic failure, inherited porphyria, bleeding disorders, severe asthma uncontrolled by corticosteroid therapy and heavy smoking (8).

According to WHO, the risk of death due to unsafe abortion complications in developing countries is hundred times higher compared to when performed under safe conditions (2).

• **Summary of comparative safety against comparators**
  1) Compared to surgical method, medical abortion has been described by some women as being ‘more discrete’ (it can be done at home) and ‘natural’. The majority of women who have already used this method would opt for the same method if needed (9).
  2) Medical treatment can reduce the number of potential complications due to unsafe surgery performed in settings where abortion is legal but unsafe.
  3) The incomplete abortion rate with mifepristone/misoprostol when used up to 9 weeks of gestation is minimal (approximately 2 to 5%) and is comparable to surgical abortion (2).
  4) Medical abortion is safe but can lead to moderate or heavy bleeding for several days and to incomplete abortion which requires further surgical abortion. Therefore, surgical abortion facility as back-up should be available where medical treatment is administered.

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

• **Range of costs of the proposed medicine**
The total cost of the treatment varies largely between countries and depends not only on the cost of drugs themselves, but also on the regimen used and the cost towards the health care facility.

**11. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)**

The mifepristone/prostaglandin regimen for first trimester medical abortion has been registered in the following countries in Europe: Austria, Belgium, Finland, France, Germany, Great Britain, Greece, Holland, Luxembourg, Norway, Romania, Spain, Sweden and Switzerland.
Further, the regimen has been registered in Azerbaijan, China, Georgia, India, Israel, Uzbekistan, New Zealand, Russia, South Africa, Tunisia, Ukraine, Vietnam and in the USA.

12. Proposed text for the WHO Model Formulary

Mifepristone combined with misoprostol
Mifepristone is an antiprogestosterone
Misoprostol is a prostaglandin; other prostaglandins can serve as an alternative.

*Tablets, mifepristone 200 mg*
*Tablets, misoprostol 200 mcg, (times 4 tablets)*

Uses: as combined regimen for first trimester (until 9 weeks) termination of pregnancy

Contraindications: chronic adrenal failure, suspected ectopic pregnancy, severe bronchial asthma uncontrolled by steroid therapy, known allergy to one of the components, hemorrhagic disorders, inherited porphyria.

Precautions:
Renal failure, liver failure and malnutrition.

Dosage: mifepristone 200 milligram followed 36-48 hours after by misoprostol 800 microgram per vaginam.

Adverse effects: nausea, vomiting, diarrhea, fever, dizziness, headaches, faintness, skin rash.

Reference


21 October 2004