

ATC codes: **G03XB51**

<b>Indication</b>	Induced abortion <span>ICD11 code: <b>JA00.1</b></span>
<b>INN</b>	Mifepristone + misoprostol
<b>Medicine type</b>	Chemical agent
<b>List type</b>	Core
<b>Additional notes</b>	Where permitted under national law and where culturally acceptable.
<b>Formulations</b>	Oral > Solid: 200 mg + 200 µg ; 200 mg [1] + 200 µg [4] in co-package
<b>EML status history</b>	First added in 2005 ( <a href="#">TRS 933</a> ) Changed in 2019 ( <a href="#">TRS 1021</a> )
<b>Sex</b>	Female
<b>Age</b>	Adolescents and adults
<b>Therapeutic alternatives</b>	The recommendation is for this specific medicine
<b>Patent information</b>	Patents have expired in most jurisdictions Read more <a href="#">about patents</a> . 
<b>Wikipedia</b>	<a href="#">Mifepristone - misoprostol</a> 
<b>DrugBank</b>	<a href="#">Mifepristone</a>  , <a href="#">Misoprostol</a> 

## Expert Committee recommendation

The Expert Committee recommended moving mifepristone-misoprostol from the complementary to the core list of the EML, and removal of the note that states that close medical supervision is required, on the basis of the strong evidence presented that close medical supervision is not required for its safe and effective use. The Committee also recommended the addition of a co-packaged presentation of mifepristone and misoprostol to the core list of the EML. Recalling that their role and responsibility is to provide WHO with technical guidance in relation to the selection and use of essential medicines, the Expert Committee noted that its mandate does not extend to providing advice on the statement “Where permitted under national law and where culturally acceptable”.

## Background

Mifepristone-misoprostol has been included on the EML for use in medical abortion since 2005. The Committee recommended listing on the complementary list with the note regarding the requirement for close medical supervision. In reviewing the recommendation by the Committee, the Director-General sought clarification from the Committee regarding the risks and benefits of mifepristone-misoprostol. The Director-General subsequently made the decision to approve listing mifepristone-misoprostol on the EML with an additional note: “Where permitted under national law and where culturally acceptable.” The current application requested the following changes to the current listing on the EML of mifepristone-misoprostol: • transfer from the complementary to the core list; • removal of the note stating “Requires close medical supervision”; • removal of the boxed text stating “Where permitted under national law and where culturally acceptable”; • addition of a co-packaged presentation of mifepristone and misoprostol.

## Public health relevance

Despite the major advances in management of abortion over the past two decades, of the 55.7 million abortions that occurred worldwide each year between 2010–2014, 30.6 million (54.9%) were considered safe, 17.1 million (30.7%) are classified as less safe and 8.0 million (14.4%) were considered least safe according to new safety classifications. 24.3 million (97%) of unsafe abortions occur in low- and middle-income countries (LMICs) (1). In LMICs, around 7 million women are admitted to hospitals annually as a result of unsafe abortion (2). Globally, between 4.7% and 13% of maternal deaths have been attributed to unsafe abortion (3).

## Benefits

Evidence for the clinical effectiveness of mifepristone-misoprostol was evaluated at the time of original listing in 2005 (4). Updated evidence was considered as part of the development process for the 2018 WHO guidelines for medical management of abortion and continues to support the effectiveness, safety and acceptability of mifepristone-misoprostol (5). Support for less medicalized service delivery of mifepristone-misoprostol exists in a number of WHO guidelines, clinical guidance and systematic reviews (5–11). Specifically, the WHO 2015 Health worker roles in providing safe abortion care and post-abortion contraception (7) and the 2018 Medical management of abortion guidance (5), state that administration of mifepristone-misoprostol does not require direct medical supervision or specialized care. WHO recommends that pregnant persons should be provided information and access to health care providers if they are experiencing signs of ongoing pregnancy or for any other medical reasons (5, 7, 8, 12). One health worker can provide the entire package, but it is equally possible for sub-tasks to be performed by different health workers and at different locations. The application states that specialized diagnostics or treatment are not needed (6). Provision of care generally requires access to quality mifepristone and misoprostol in the correct dosages, instructions on how to use them (including dating of gestational age) and information about how to recognize complications (e.g. in the event of very heavy and/or prolonged bleeding) and where to seek help. Ultrasound scanning is not routinely required (5–8), and routine use of antibiotics and testing for sexually transmitted infections is not recommended. In the event of undiagnosed ectopic pregnancy, heavy, ongoing bleeding and/or retained products of conception that may not evacuate on its own, the pregnant person may require referral to a higher level care (6–8). Evidence supports safe and effective provision of medical abortion for pregnancies less than 12 weeks uterine size by the following health care cadres: auxiliary nurses, auxiliary nurse midwives, nurses, midwives, associate and advanced associate clinicians, non-specialist and specialist doctors (5–9, 13–17). It is recommended that every primary care health service delivery point have staff (regardless of their cadre) trained and competent to take a medical history, perform a bimanual and abdominal examination and establish a referral network with higher level facilities and/or providers who are available to manage complications in the rare event that they may arise. The application stated that desired benefit of co-packaged mifepristone-misoprostol is to ensure availability of quality-assured products with consistent and clear dosing. A recent study of the provision of medical abortion and post-abortion contraception by mid-level health care providers in Kyrgyzstan involved training midwives and family nurses to provide medical abortion with co-packaged mifepristone-misoprostol (18). Results demonstrated that trained midwives and nurses can provide medical abortion safely and effectively. Although the study did not compare co-packaged mifepristone-misoprostol with individually packaged drugs, the authors recommended registration and market availability of high quality co-packaged mifepristone-misoprostol as a strategy to facilitate the scale up of safe abortion in Kyrgyzstan.

## Harms

Evidence for the safety of mifepristone-misoprostol was evaluated at the time of original listing in 2005 (4). Recently published safety data from the United States reported an estimated mifepristone-associated mortality rate of 0.00063% (19). Studies including mifepristone-misoprostol medical abortions among more than 423 000 persons globally reported very low rates (0.01 to 0.7%) of non-fatal serious adverse events such as hospital admission, blood transfusion or serious infection after use of mifepristone (19). In addition, a pooled analysis of serious adverse reactions including data from 30 966 clinical study participants presenting for mifepristone-misoprostol medical abortion through 70 days gestation found no differences in rate or type of serious adverse reaction by geographical location (20). Serious adverse reaction rates were reported in <0.5% of study participants and include atypical presentation of infection, sepsis and prolonged heavy bleeding/hemorrhage (20). These events were typically treatable without permanent sequelae. The 2015 WHO recommendations on health worker roles in providing safe abortion care

and post-abortion contraception highlight that the most commonly experienced non-life threatening side-effects can be managed in primary care and outpatient settings by various cadres of health care providers (7). Evidence suggests that the provision of medical abortion by mid-level providers has no impact on the safety or efficacy of the abortion process (21). Self-management of medical abortion with mifepristone-misoprostol without the direct supervision of a health care provider is recommended in specific circumstances, in which pregnant persons have the appropriate information and access to health services should they be wanted or required (5–7, 22).

### Additional evidence

N/A

### Cost / cost effectiveness

The price of individual and co-packaged mifepristone and misoprostol varies globally. The legal status of abortion, willing marketers and distributors and a perceived sustainable market all impact the cost to the buyer. Market flexibility is being regulated by the increasing number of new products in markets – both individual and co-packaged products. It is hoped that increasing access to quality co-packaged medicines for medical abortion will drive prices down. The application stated that when purchased individually, the average cost of mifepristone and misoprostol for one medical abortion ranges from US\$ 4.19 to US\$ 10.03, while costs for the co-packaged product range from US\$ 3.75 to US\$ 11.75.

### WHO guidelines

WHO Safe abortion: Technical and policy guidance (6) was first issued in 2003 and updated in 2012. It includes recommendations for clinical care, while also addressing policy, programmatic and health systems considerations in the provision of safe abortion. WHO Clinical practice handbook for safe abortion (8) was issued in 2014. It provides guidance to providers with requisite skills and training necessary to provide safe abortion and/or treat complications of unsafe abortion. WHO Health worker roles in providing safe abortion and post-abortion contraception (7) was issued in 2015 and contains recommendations on the roles of various health workers in the provision of abortion care, as well as self-management of medical abortion. WHO Medical management of abortion (5) guidelines issued in 2018 includes the following recommendations on medical abortion regimens for management of induced abortion: For the medical management of induced abortion at less than 12 weeks gestation, the 2018 WHO guidelines recommend the use of 200 mg mifepristone administered orally, followed one to two days later by 800 micrograms misoprostol administered vaginally, sublingually or buccally. The minimum recommended interval between use of mifepristone and misoprostol is 24 hours (strong recommendation, moderate certainty evidence). For the medical management of induced abortion at  $\geq 12$  weeks of gestation, the 2018 WHO guidelines suggest the use of 200 mg mifepristone administered orally, followed one to two days later by repeat doses of 400 micrograms misoprostol administered vaginally, sublingually or buccally every three hours. The minimum recommended interval between use of mifepristone and misoprostol is 24 hours (weak, conditional, discretionary or qualified recommendation, moderate certainty evidence).

### Availability

Mifepristone and misoprostol, both individually and co-packaged are available globally.

### Other considerations

The Committee noted the large number of letters of support received in relation to this application.

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