

# Misoprostol for maternal health

## Description

Misoprostol can be used for a number of obstetric indications that address maternal health concerns. Misoprostol acts as a uterotonic by stimulating strong contractions of the uterus and also softens and dilates the cervix, similar to the natural process of labor. Its uses related to maternal health are many and include the prevention and treatment of postpartum hemorrhage, labor induction, treatment of incomplete abortion and miscarriage, induced abortion, treatment of missed abortion, treatment of intrauterine fetal death, and cervical ripening before delivery or uterine instrumentation.

Dosing regimens vary depending on the medical indication. For labor induction and cervical ripening before delivery, the dose can be as low as 25 µg; however, other indications require a dose of between 400 and 800 µg. Recommended routes of administration are oral, sublingual, rectal, or vaginal. In 2012, the International Federation of Gynecology and Obstetrics (FIGO) revised dosage guidelines for all obstetric indications.<sup>1</sup> Misoprostol is available in tablet form, and marketed products typically have a shelf life of 18 to 36 months when stored below 25°C to 30°C (77°F to 86°F) in a dry area.

## Efficacy

**For the prevention of postpartum hemorrhage (PPH):** Misoprostol is an effective uterotonic in situations where use of oxytocin or other injectable uterotonics that require refrigeration and administration by a skilled provider is not feasible. For these reasons, misoprostol can be especially useful in home deliveries. In a multicenter study conducted in hospitals, oxytocin performed marginally better than oral misoprostol in controlling blood loss.<sup>2</sup> In a study of women delivering at home in India,

oral misoprostol was associated with a significant reduction in the rate of postpartum hemorrhage compared to women not using a uterotonic.<sup>3</sup> A significant reduction in PPH was also observed with oral misoprostol when administered by traditional birth attendants during home deliveries in Pakistan.<sup>4</sup>

The 2012 World Health Organization (WHO) recommendations for the prevention and treatment of postpartum hemorrhage and the 2012 WHO Priority Life-saving Medicines for Women and Children state that in settings where oxytocin is unavailable or cannot be safely used, the use of oral misoprostol (600 µg) is recommended for prophylaxis.<sup>5,6</sup> WHO's 17th Model List of Essential Medicines includes the use of 600-µg oral misoprostol for prevention of PPH.<sup>7</sup>

**For the treatment of PPH:** In women who were given prophylactic oxytocin as part of the active management of the third stage of labor, misoprostol and oxytocin were found to be clinically equivalent when used to stop excessive postpartum bleeding.<sup>8</sup> In women not exposed to prophylactic oxytocin, oxytocin was found to be more effective at controlling bleeding within 20 minutes than misoprostol, but researchers concluded that 800-µg sublingual misoprostol might be a suitable first-line treatment in settings in which use of oxytocin is not feasible.<sup>9</sup> WHO recommends the use of 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.<sup>5</sup>

**For the treatment of incomplete abortion and miscarriage:** The efficacy of misoprostol to treat incomplete abortion and miscarriage is between 91 to 99 percent, equivalent to the use of manual vacuum aspiration.\* Medical management of incomplete abortion and miscarriage with misoprostol provides a good opportunity to scale up post-abortion care

\* For a complete list of references and discussion, please refer to the Post-abortion care (PAC) Service Delivery Toolkit located at [www.vsinnovations.org/resources.html](http://www.vsinnovations.org/resources.html) or <http://www.ipas.org/en/What-We-Do/Comprehensive-Abortion-Care/Elements-of-Comprehensive-Abortion-Care/Medical-Abortion--MA-/Medical-Abortion--MA--Supply-Guidance/Postabortion-Care-Educational-Resources.aspx>.

services.\*\* WHO's 17th Model List of Essential Medicines and its Priority Life-saving Medicines for Women and Children include the use of misoprostol for this indication.<sup>6,7</sup>

**For induced abortion\*\*\*:** Effectiveness of misoprostol-alone regimens for early-term medical abortion range from 76 to 96 percent. Technical and policy guidance for health systems, revised in 2012, recommends the use of misoprostol for induced abortion when mifepristone is not available and provides dosage guidelines for pregnancies up to 12 weeks gestational age, from 12 to 24 weeks, and beyond 24 weeks.<sup>10</sup> Though not as effective as the combination of mifepristone and misoprostol, misoprostol is more widely available than mifepristone and has been used safely and successfully for medical abortion around the world.<sup>11</sup>

**For labor induction:** Cochrane Reviews have concluded that oral misoprostol is more effective than placebo and at least as effective as vaginal dinoprostone for induction of labor with doses not exceeding 50 µg; similarly, while vaginal misoprostol is more effective than other conventional methods, low-dose oral misoprostol is preferable.<sup>12,13</sup> WHO and FIGO recommend the use of oral (25 µg, at two-hour intervals) or vaginal (25 µg, at six-hour intervals) misoprostol for the induction of labor.<sup>1,14</sup>

### Current program/sector use

In developing countries, programs to introduce or expand the use of misoprostol into the health system for some obstetric indications are being implemented. Misoprostol is included on the national essential medicines lists in more than 20 countries.

WHO recommends that misoprostol can be used by community health care workers and lay health workers for PPH prevention when skilled birth attendants are not present.<sup>5</sup> A similar recommendation for lay health workers is included in WHO's 2012 guidelines on optimizing health worker roles for maternal and neonatal health, though advanced provision of misoprostol to pregnant women is deemed a priority research area.<sup>15</sup>

For the prevention of PPH, studies in Afghanistan, Bangladesh, and Nepal show that women can use misoprostol consistently and safely (even for twin

deliveries) when the drug is distributed by community health workers to women planning to deliver at home.<sup>16,17,18</sup> Programs in Bangladesh, Ethiopia, Kenya, Mozambique, Nigeria, Senegal, Tanzania, Uganda, and Zambia have shown that distribution at antenatal care visits and by community health workers is effective and that misoprostol is used safely and correctly at home deliveries.<sup>19</sup> Some countries are now taking steps to scale up the use of misoprostol for PPH prevention in national safe-motherhood programs.

Pilot PAC programs in Mozambique and Rwanda have shown that misoprostol can be safely used as a complementary method to manual vacuum aspiration (MVA) for treatment of incomplete abortion and miscarriage (evacuation of the uterus), particularly at lower-level health facilities where the use of MVA may not be feasible, or there may not be health workers trained in its use.<sup>20</sup>

In clinical settings globally, misoprostol is commonly used off label for induction of labor and cervical ripening, and in combination with mifepristone for medical abortion, where legally permissible.<sup>21</sup>

### Manufacturer/supplier

More than 50 branded and non-branded generic versions of 200-µg misoprostol tablets are manufactured by pharmaceutical companies in high-, middle-, and low-income countries including Argentina, Bangladesh, Brazil, Chile, China, Egypt, France, India, Mexico, Pakistan, Peru, Russia, South Korea, and the United States.<sup>22</sup> Some of these manufacturers are making products for export to low- and middle-income countries, but many only make products for their local markets. Cytotec® (manufactured by Pfizer) is the most widely available misoprostol product. The few manufacturers of the 25-µg tablet include Cipla Pharmaceuticals (India), Adwia Pharmaceuticals (Egypt), and Hebron Pharmaceuticals (Brazil).

Misoprostol is eligible for the WHO's Prequalification of Medicines Programme, but no product is yet prequalified.<sup>23</sup> As part of its Quality Assurance Policy for Reproductive Health Medicines, the United Nations Population Fund (UNFPA) has set up an Expert Review Panel (ERP) to assess whether reproductive health products (including misoprostol) from manufacturers that apply for

\*\* Further information on the treatment of incomplete abortion with misoprostol and service delivery guidelines for integrating misoprostol into PAC services can be found at <http://vsinnovations.org/resources.html> or <http://www.ipas.org/ma/mpactoolkit> and <http://gynuity.org/resources/info/guidebook-on-misoprostol-for-treatment-of-incomplete-abortion/>.

\*\*\* For more information on misoprostol for induced medical abortion, please see the Caucus brief Mifepristone and Misoprostol for on Medical Abortion.

WHO prequalification could be recommended for use before achieving prequalification.<sup>24</sup> A product made by Exelgyn (France) has passed the ERP process, but is only registered for use with mifepristone for termination of pregnancy. Efforts are underway to provide technical assistance to generic manufacturers of misoprostol products that can be registered for other obstetric indications, with the aim of building their capacity to pass the ERP process and achieve WHO prequalification.<sup>25</sup>

## Registration status

Registration, or market approval of a drug by a country's drug regulatory agency, grants permission for a product from a specific manufacturer to be marketed in that country by a pharmaceutical distributor for the medical indications for which the application was made. The registration status of misoprostol varies. Misoprostol is most commonly registered for prevention and treatment of gastric ulcers; Cytotec® is registered in more than 80 countries for these two indications. In many countries, misoprostol may be legally used off label for obstetric indications.

Misoprostol is increasingly being registered for obstetric indications. Exporting manufacturers that have registered products for obstetric indications, mostly in sub-Saharan Africa and South Asia, include Acme Formulations (India), Cipla Pharmaceuticals (India), Sigma Pharmaceuticals (Egypt), Square Pharmaceuticals (Bangladesh), Zizhu Pharmaceuticals (China), and Fourtts Laboratories (India), and there are likely to be others.

Products are registered for obstetric indications in more than 20 countries, including Bangladesh, Bolivia, Cambodia, Ethiopia, India, Kenya, Malawi, Mali, Mozambique, Myanmar, Nepal, Pakistan, Senegal, Somaliland, Sudan, Tanzania, Uganda, and Zambia. More registrations are expected in the coming years in response to increasing demand. 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. The indications for which the drug is granted approval usually depend on the level of commitment and willingness of governments to integrate misoprostol into safe-motherhood programs. More information on the global status of misoprostol registration can be found at <http://www.vsinnovations.org/resources.html>.

## Public-sector price agreements

There are no global public-sector price agreements for misoprostol. Governments can purchase a misoprostol product that is registered in their country and can negotiate the price with the distributor that holds the market approval.

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