(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☐ No ☐

Please provide brief details:
Postpartum hemorrhage is an important cause of maternal mortality and morbidity. It accounts for nearly one quarter of maternal deaths in developing countries. Management of obstetric haemorrhage involves early recognition, assessment and resuscitation. Various methods are available to try to stop the bleeding – from pharmacological methods to aid uterine contraction (e.g., oxytocin, ergometrine and prostaglandins) to surgical methods to stem the bleeding (e.g., balloon tamponade, compression sutures or arterial ligation).
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 to treat PPH immediately.

(2) Have all important studies that you are aware of been included in the application?

Yes ☐ No ☐

Please provide brief comments on any relevant studies that have not been included:

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☐ No ☐

Briefly summarise the reported outcomes (e.g. clinical, surrogate, other) and comment, where possible, on the magnitude of clinical benefit associated with use of the medicine:
When misoprostol was used alone to treat PPH, the data show, that oxytocin was found to work significantly better than misoprostol for PPH treatment among women who did not receive prophylactic uterotonic. And that misoprostol was found to be similar in effectiveness to IV oxytocin for treatment of primary PPH in women receiving prophylactic oxytocin.
-While there appears to be no advantage to adjunct use of misoprostol for PPH treatment

(4) Is there evidence of efficacy in diverse settings and/or populations?
Studies were done in diverse settings (Africa, Asia and Latin America)

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes  □  No  □

Please provide brief details:
- Women who receive misoprostol during the third stage of labor are at risk for elevated body temperature, shivering, nausea and vomiting.
- Studies on postpartum use of misoprostol show the rates of shivering and fever to be related, and to be dose- and route-dependent. Temperature above 39°C was observed in 8.3, 8.3, and 45% of women given 200, 400, and 600 µg sublingual misoprostol, respectively. Compared to placebo. Higher rates of shivering and elevated body temperature are also associated with oral and sublingual routes of administration.
- The proposed dose of misoprostol for treatment of PPH is 800 µg sublingually. Two studies testing an 800 mcg 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. Rates of fever after treatment were also more common in the misoprostol group (34% vs. 10%, respectively).
- In several PPH prevention and treatment studies, misoprostol has been associated with fever greater than 40.0°C (104°F). It is more with higher doses.
- A systematic review (Hofmeyr 2011) included 78 studies (59,216 women): PPH prevention (71) and PPH treatment (8) concluded that misoprostol does not appear to increase or reduce severe morbidity (excluding hyperpyrexia) when used to prevent or treat PPH. Misoprostol did not increase or decrease maternal mortality. However, misoprostol is associated with an increased risk of pyrexia, particularly in dosages of 600 µg or more.

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes  ■  No  □

Please provide brief details:
Not for administration but for monitoring and management of side effects (shivering and pyrexia).

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)
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.

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.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes [ ] No [ ]

Please provide brief details:

In WHO guidelines for the prevention and treatment of PPH (WHO 2012a):
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.

(9) Please comment briefly on issues regarding cost and affordability of this 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.

(10) Any additional comments?

(11) Please summarise the action you propose the Expert Committee takes.

The application does not add new information as regards efficacy and safety in comparison to previous application (2013). There is no strong justification to change the previous decision of not adding misoprostol for treatment of PPH. To recommend misoprostol for prevention and treatment of PPH could divert the attention or reduce attempts to implement oxytocin availability. The argument that misoprostol administration does not require needles, syringes and tools to ensure safe injection, is not valid in this situation because gaining an access to IV line, resuscitation, assessment to
diagnose the cause of bleeding and prompt implementation of all evidence based interventions (medical and surgical) are all crucial to save the patient. PPH is a life threatening condition and can lead to death very rapidly (two hours).