Expert peer review on application for inclusion of misoprostol for PPH treatment

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes   No (if no, please provide reference and information)
   Yes
b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   - 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 uterotonics. 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.

c. Please provide any additional relevant information with reference

2. Assessment of safety
a. Have all relevant studies on safety been included
   Yes   No (if no, please provide reference and information)
   Yes
b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   - 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. Compared to placebo, a recent meta-analysis shows that the risk of pyrexia is increased three-fold with 400 mcg misoprostol and six-fold with 600 mcg misoprostol when administered during the third stage of labor. 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 ug 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.

c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
   a. Have all relevant data on safety provided
      Yes    No (if no, please provide reference and information)
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

The International Drug Price Indicator Guide 2011 published by Management Sciences for Health (MSH), was used to obtain present prices of misoprostol. The median supplier price listed was USD 0.3939 per 200μg tablet of misoprostol (USD 1.58 per dose for treatment). The median price paid by the three buyers listed was USD 0.09 per tablet (range USD 0.0564-0.17); or USD 0.36 per dose for PPH treatment.

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?
   Yes, but for other indications.

4. Assessment of public health need
   a. Please provide the public health need for this product (1-2 sentences)

   Postpartum hemorrhage is an important cause of maternal mortality and morbidity. It accounts of 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., oxytocinon, ergometrine and prostaglandins) to surgical methods to stem the bleeding (e.g., balloon tamponade, compression sutures or arterial ligation).
b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

-WHO recommendations on the Prevention and Treatment of Postpartum Hemorrhage (2012), the WHO noted: “Intravenous oxytocin is the recommended uterotonic drug for the treatment of PPH; however, in settings where IV oxytocin is not available, 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.”


5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

-Not for administration but for monitoring and management of side effects.

6. Is the proposed product registered by a stringent regulatory authority?
   Yes   No

   Yes, but not for this indication (Treatment of PPH)

7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)

For the use of 800 micrograms misoprostol sublingually as a first line treatment of PPH, the benefit/risk ratio is in favour of oxytocin use as a first line treatment.

In addition, there is no evidence to support the safety of 800 micrograms misoprostol dose for treatment of PPH when given to women who have previously received prophylactic misoprostol 600 micrograms orally. This scenario is more likely to occur in settings where oxytocin is not available.

To recommend misoprostol for prevention and treatment of PPH could divert the attention or reduce attempts to implement oxytocin availability. 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., oxytocinor, ergometrine and prostaglandins) to surgical methods to stem the bleeding (e.g., balloon tamponade, compression sutures or arterial ligation). Even among the pharmacological interventions, the need for parenteral uterotonics is more compelling, as the sublingual route may be not feasible in many cases (vomiting, irritability, loss of consciousness). 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 is crucial in these cases. PPH is a life threatening condition and can lead to death very rapidly (two hours). So all aspects of managements mentioned above should be available.

For these reasons, I recommend not to list treatment of PPH in the note to this inclusion in the Model EML.