Expert peer review on application for the addition of the PPH treatment indication to Misoprostol

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes ✓
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      The two largest multi-center, large-scale double-blinded, placebo-controlled, randomized trials compared the effectiveness, safety, and acceptability of 800 mcg sublingual misoprostol to 40 IU intravenous oxytocin among 1,786 women diagnosed with PPH after vaginal delivery due to suspected uterine atony.

      The data show misoprostol to be similar in effectiveness to IV oxytocin for treatment of primary PPH in women receiving prophylactic oxytocin; however, oxytocin was found to work significantly better than misoprostol when used for PPH treatment among women who did not receive prophylactic uterotonics.

      In both trials, whether treatment was with oxytocin or misoprostol, nine out of ten women had their bleeding successfully controlled within 20 min of drug administration (Blum, et al. 2010; Winikoff, et al. 2010).

   c. Please provide any additional relevant information with reference
      NA

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes ✓
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      The most common side effects associated with the postpartum administration of misoprostol are shivering and pyrexia. 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, which achieve a higher and quicker maximum plasma concentration than vaginal or rectal administration. These side effects are transient, short-lived and not life-threatening.
Other reported side effects are nausea, vomiting, diarrhoea, and abdominal cramps. Abdominal cramps usually develop within the first few hours and may start as early as 10 minutes after administration. Diarrhoea is the most common gastrointestinal side effect and it is usually mild and self-limiting within a day; vomiting usually resolves in less than 6 hours. These events seem to be associated to determined doses and routes. They are more common after oral or sublingual administration.

A few maternal deaths were reported in a recent large meta-analysis, which had occurred during misoprostol use for management of PPH. Some deaths were due to severe haemorrhage, while others did not seem to be directly related to haemorrhage.

c. Please provide any additional relevant information with reference

NA

3. Assessment of cost and availability
   a. Have all relevant data on cost been provided
      Yes ✓
   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)

Supplier price:

<table>
<thead>
<tr>
<th>200 microgr tablet</th>
<th>USD 0.3939</th>
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<tr>
<td>1 treatment dose</td>
<td>USD 1.58</td>
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No directly applicable cost-effectiveness analysis has been provided. The case is made by the applicant that cost-effectiveness in comparison to the i/v uterotonics may not be relevant as these are not an alternative in the setting where misoprostol would be used.

c. Please provide any additional relevant information with reference

NA

d. Is the product available in several low and middle income countries?

Yes

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

Postpartum hemorrhage is one of the largest contributors to maternal morbidity and mortality in low resource countries and accounts for nearly one quarter of all maternal deaths worldwide.

A more effective common alternative, oxytocin, requires specific transport and storage conditions and skilled administration.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable
Yes. WHO recommendations for the prevention and treatment of PPH, 2012: for PPH prevention in settings where skilled birth attendants are not present and oxytocin is unavailable and for PPH treatment if intravenous oxytocin is unavailable or if the bleeding does not respond to oxytocin.

5. Are there special requirements for use or training needed for safe/effective use?

There are less stringent requirements for transport, storage and administration than for oxytocin. Basic birth attendant training is necessary.

6. Is the proposed product registered by a stringent regulatory authority?

   No ✓

   The reviewer is not aware of any stringent regulatory authority approval of the product in this indication.

7. Any other comments

   NA

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

   Based on the results of the recent trials submitted by the applicant the Committee is recommended to list the indication of “PPH treatment if intravenous oxytocin is unavailable”.

Misoprostol PPH treatment