Expert peer review on application for the deletion of Misoprostol (PPH prevention indication)

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)

   Oral or sublingual misoprostol compared with placebo is effective in reducing severe PPH (oral: seven trials, 6225 women, not totalled due to significant heterogeneity; sublingual: risk ratio (RR) 0.66; 95% confidence interval (CI) 0.45 to 0.98; one trial, 661 women) and blood transfusion (oral: RR 0.31; 95% CI 0.10 to 0.94; four trials, 3519 women).

   Compared with conventional injectable uterotonics, oral misoprostol was associated with higher risk of severe PPH (RR 1.33; 95% CI 1.16 to 1.52; 17 trials, 29,797 women) and use of additional uterotonics, but with a trend to fewer blood transfusions (RR 0.84; 95% CI 0.66 to 1.06; 15 trials; 28,213 women). Additional uterotonic data were not totalled due to heterogeneity


   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)

   Misoprostol use for prevention and treatment of postpartum haemorrhage (PPH) is consistently associated with increased risk of shivering and pyrexia, reported in the majority of clinical trials as a transient and dose-dependent finding. Misoprostol use was associated with significant increases in shivering and a temperature of 38º Celsius compared with both placebo and other uterotonics in the above Cochrane review.

   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


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

      NA (application for deletion)

   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)

      NA

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 .

      PPH is one of the leading contributors to maternal morbidity and mortality in low-resource settings. The product has a role in preventing PPH in the circumstances where standard uterotonics are not available or accessible.

   b. Do guidelines (especially WHO guidelines) recommend this product?

      Yes. WHO recommendations for the prevention and treatment of postpartum haemorrhage 2012.

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

   Not above the standard training for birth attendants.
6. Is the proposed product registered by a stringent regulatory authority?
   No (there is no assurance available to the reviewer that the clinical data in this indication have been assessed, i.e. a positive benefit-risk balance established by a stringent regulatory authority)

7. Any other comments
   NA

8. What is your recommendation to the committee (please provide the rationale)
   Considering the recent guideline by the WHO and the much more positive interpretation of the data by other groups (e.g. the authors of the Cochrane review) the Committee is recommended to keep the listing as it is.