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

Yes ☐ No ☐

Please provide brief details:
A WHO systematic review on the cause of maternal deaths identified obstetric haemorrhage as the largest cause of maternal death in Africa and Asia where the majority of maternal deaths occur (Khan 2006). Prevention of PPH with appropriate, evidence-based interventions such as oxytocin and misoprostol when oxytocin is not available could prevent a substantial proportion of deaths in these two regions.

(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:

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). Oral misoprostol reduced the need for additional uterotonics but not significantly (Tunçalp et al. (2012)).

(4) Is there evidence of efficacy in diverse settings and/or populations?

Yes ☐ No ☐

Please provide brief details:
Studies have been conducted in diverse settings in 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:
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. Oral misoprostol 600mcg was consistently associated with higher rates of prostaglandin-related side-effects such as nausea, vomiting, diarrhoea as well as for ‘any’ shivering, severe shivering and pyrexia (greater than 38 °C) when compared with placebo. No adverse effects has been reported in the mothers or neonates

ADDITIONAL CONSIDERATIONS:

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

Yes ☐ No ☐
Oral intake of misoprostol makes it less demanding than injectable uterotonics. But needs understanding and management of the possible side effects.

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

Yes [ ] No [ ]

Please provide brief details:

Misoprostol is not approved for PPH prevention by stringent regulatory agencies such as US FDA, UK MHRA. In 2014 EMA approved misoprostol for the treatment of postpartum haemorrhage.

Developing countries: Misoprostol for prevention and treatment of post-partum haemorrhage has been licensed in several developing countries (Holden 2009).

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

Yes [ ] No [ ]

Please provide brief details:

The most recent WHO guidelines for the prevention and treatment of PPH (WHO 2012a) recommend the universal use of uterotonics during the third stage of labour to prevent PPH. The recommended uterotonics are:

1. oxytocin (Strong recommendation, moderate-quality evidence);
2. other injectable uterotonics (if appropriate ergometrine/methylergometrine or the fixed drug combination of oxytocin and ergometrine) or oral misoprostol in settings where oxytocin is not available (Strong recommendation, moderate quality evidence);
3. misoprostol administered by community health care workers and lay health workers where skilled birth attendants are not
present and oxytocin not available (Strong recommendation, moderate quality evidence)

(9) Please comment briefly on issues regarding cost and affordability of this medicine.
Not mentioned in the application.

(10) Any additional comments?

(11) Please summarise the action you propose the Expert Committee takes.
The application did not provide any new information which justify changing the previous decision of EML. Misoprostol is to be kept in the List, for the prevention of PPH in settings where parenteral uterotonics are not available or feasible. Oxytocin is the first line uterotonic to be used based on efficacy and safety profile. Unfortunately, oxytocin is not available nor is safe injection feasible in many settings, especially in communities where most of the deliveries are outside hospitals. In such settings, we are obliged to offer an alternative to these women though less effective than oxytocin, that is misoprostol. Oral administration and heat stability are other advantages. However governments and funding agencies should do more efforts to make oxytocin available for women in all delivery settings.