22. Medicines for reproductive health and perinatal care

22.3. Uterotonics

Misoprostol

**Essential medicine status**

**Expert Committee recommendation**

The Committee did not recommend the deletion of the indication for prevention of PPH from the listing of misoprostol from EML. The Committee considered that the new evidence presented in this re-submission was insufficient to support any change to the current listing. The Committee reiterated that misoprostol remains an effective alternative for prevention of PPH in resource-poor, community and rural settings where oxytocin is unavailable or cannot be safely administered. The listing of misoprostol on the EML supports its appropriate use in such settings and is consistent with the 2018 WHO recommendations for uterotonics for the prevention of PPH.

**Background**

The application requested the deletion of misoprostol from the EML for the indication of prevention of postpartum haemorrhage. Misoprostol was added to the EML in 2011 for prevention of PPH in settings where parenteral uterotonics are not available or feasible. It was, and remains listed with a conditional note specifying that its use in PPH is limited to circumstances where oxytocin is not available or cannot be safely used. This was the fourth application from Drs Sevcikova and Pollock requesting deletion of misoprostol from the EML for prevention of PPH. Most recently in 2017, the Expert Committee did not recommend deletion, noting that very few new clinical data were included in the application. The Committee considered that the evidence presented was insufficient to support deletion. The Expert Committee once again acknowledged that misoprostol is less effective than oxytocin infusion and is associated with adverse events, particularly vomiting and shivering. The circumstances of use have not changed; misoprostol remains an alternative for the prevention of PPH in resource-poor, community and rural settings where intravenous oxytocin is not available or cannot be safely administered.
Obstetric haemorrhage, especially PPH, is responsible for more than a quarter of all maternal deaths worldwide (3). In most low-income countries, PPH is the leading cause of maternal deaths.

The same evidence presented in the 2017 application was included in the current application. Only evidence not previously considered by the Committee is presented here. To update the evidence base presented and considered in previous applications, the current application undertook a literature search for randomized controlled trials (RCTs) assessing misoprostol use in community and home birth settings in low- and middle-income countries (LMICs) published between November 2016 and November 2018. This search identified two systematic reviews (1, 4), one of which was excluded as it included trials conducted in hospitals (4). No additional RCTs conducted in low-resource settings were identified. The application presented results extracted from a sub-group analysis from the Cochrane systematic review by Gallos et al for the comparison of misoprostol versus placebo or no treatment from three trials conducted in the community setting (5–7). Efficacy outcomes and effect size: Death: RR 1.00 [95%CI 0.10 to 9.59] PPH ≥ 1000 ml: RR 0.59 [95%CI 0.39 to 0.88] Blood transfusion: RR 0.14 [95%CI 0.02 to 1.15] Severe maternal morbidity: RR 1.00 [95%CI 0.14 to 7.05] PPH ≥ 500 ml: RR 0.73 [95%CI 0.56 to 0.96] Additional uterotonics: RR 0.50 [95%CI 0.12 to 1.98] Blood loss: MD −43.79 [95%CI −58.09 to −29.49] Change in haemoglobin: MD −2.12 [95%CI −3.46 to −0.77] Safety outcomes and effect size: Nausea: RR 1.12 [95%CI 0.74 to 1.70] Vomiting: RR 1.27 [95%CI 0.80 to 2.01] Headache RR 0.94 [95%CI 0.32 to 2.77] Shivering RR 2.71 [95%CI 2.33 to 3.15] Fever RR 2.87 [95%CI 0.90 to 9.18] Diarrhoea RR 3.11 [95%CI 1.28 to 7.51] (RR: risk ratio, MD: mean difference) Gallos et al reported no important differences were identified in the subgroup analysis by hospital or community setting (1). Commenting on the quality of available evidence, the application noted that all community studies have important shortcomings either due to small numbers; use of alternative uterotonics in the control arm; confounding due to management practice and subjective assessment; and with one exception (6) (in which the numbers were very small), exclusion of high-risk women. PPH incidence fell in both the control and intervention groups in both the trials (5, 7) that informed the 2011 decision to add misoprostol to the EML. This suggests factors other than misoprostol use are crucial in determining outcomes.

No new safety data (beyond that presented above) were included in the current application.

The 2018 WHO recommendations state that as misoprostol is inexpensive and can also be used by lay health workers in community settings, it is associated with moderate savings and is probably cost-effective, especially when implemented in settings with a shortage of skilled health personnel (8).

The 2018 WHO recommendations for uterotonics for the prevention of PPH (8) recommend use of an effective uterotonic during the third stage of labour for all births. Misoprostol 400 µg or 600 µg, orally is a recommended option for all births.

