Misoprostol

Essential medicine status ✓

ATC codes: G02AD06

Indication	Postpartum haemorrhage ICD11 code: JA43.Z
INN	Misoprostol
Medicine type	Chemical agent
List type	Core
Additional notes	For the prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used.
Formulations	Oral > Solid: 200 µg
EML status history	First added in 2011 (TRS 965) Changed in 2015 (TRS 994) Changed in 2017 (TRS 1006) Changed in 2019 (TRS 1021)
Sex	Female
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Misoprostol
DrugBank	Misoprostol

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 (2).

Public health relevance

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.

Benefits

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.

Harms

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

Cost / cost effectiveness

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).

WHO guidelines

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.

1. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018;12:CD011689.
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.
3. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.
4. Abd El Aziz MA, Iraqi A, Abedi P, Jahanfar S. The effect of carbetocin compared to misoprostol in management of the third stage of labor and prevention of postpartum hemorrhage: a systematic review. Syst Rev. 2018;7(1):170.
5. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006;368(9543):1248–53.

6. Hoj L, Cardoso P, Nielsen BB, Hvidman L, Nielsen J, Aaby P. Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial. BMJ. 2005;331(7519):723.
7. Mobeen N, Durocher J, Zuberi N, Jahan N, Blum J, Wasim S et al. Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial. BJOG. 2011;118(3):353–61.
8. WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1, accessed 29 September 2019.