1. **Summary statement of the proposal for inclusion, change or deletion**

That the Expert Committee review and rescind the decision of the 18th Expert Committee on the Selection and use of Essential Medicines March 2011 to add misoprostol for the prevention of postpartum haemorrhage to the Essential Medicines List, on the basis that evidence of efficacy is lacking (see Chu et al. 2012 for a critical appraisal of existing evidence, enclosed).

2. **Name of the focal point in WHO submitting or supporting the application (where relevant)**

N/A

3. **Name of the organization(s) consulted and/or supporting the application**

N/A

4. **International Nonproprietary Name (INN, generic name) of the medicine**

Misoprostol

5. **Formulation proposed for inclusion; including adult and paediatric (if appropriate)**

We request the Committee delete the following clause: “, and for prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used” from the Section 22.1 Oxytocics from the current WHO Model List of Essential Medicines (17th list).

6. **International availability - sources, if possible manufacturers and trade names**

N/A

7. **Whether listing is requested as an individual medicine or as an example of a therapeutic group**

N/A

8. **Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)**

N/A

9. **Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)**

N/A

10. **Summary of comparative effectiveness in a variety of clinical settings:**

   - Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)
Medline and Embase databases were searched for clinical studies assessing misoprostol use in community and home birth settings in low- and middle-income countries (defined by World Bank classification) published before November 2011 using search terms 'PPH'; bleeding in TSL; misoprostol; RCTs; and ‘prevention’. The database search revealed two systematic reviews and further studies were also identified from the sources. Studies were excluded if duplicate, considering injectable prostaglandins, non-RCTs, not reported in English, in high-income and hospital settings. Of the 172 studies only six matched the inclusion criteria (Enclosure 1).

Our search of the databases identified the same four key studies examined in the Unedited report of the 18th Expert Committee on the Selection and Use of Essential Medicines (1): Walraven et al. 2008 (2; reporting on the same RCT as Walraven et al. 2005 (3)); Hoj et al. 2005 (4); Derman et al. 2006 (5); and Mobeen et al. 2010 (6). These studies are also included in the recent Cochrane Systematic Cochrane Review (Enclosure 2).

We critically appraised the studies using a framework adapted from Fowkes and Fulton, Critical Appraisal Skills Programme and Cochrane guidelines for systematic review with respect to study design (setting, number of participants, level of blinding, risk status of women, methods to measure outcomes), intervention (route and dose of misoprostol, the control arm, attendance at birth, management used in TSL) and the outcomes of the studies.

• Summary of available data* (appraisal of quality, outcome measures, summary of results):

See below

• Summary of available estimates of comparative effectiveness

It is not possible to estimate overall effectiveness of misoprostol, or it comparative effectiveness, due to significant heterogeneity in the study design of existing studies.

The four key trials used 600μg misoprostol in the intervention arm; three assessed misoprostol alongside components of active management of the third-stage labour (AMTSL), two used expectant management of labour and one allowed birth attendants to choose management practice. The three AMTSL studies showed no significant differences in PPH incidence or referral to higher centres and only one study showed significant decrease in severe PPH using misoprostol. One expectant management study and the choice of management by birth attendants study found significant decreases in PPH incidence with misoprostol. All studies showed significantly increased risk of shivering with misoprostol.

All studies have important shortcomings either due use of alternative uterotonics in the control arm, confounding management practices, and subjective assessment or, with one exception, exclusion of high-risk women. PPH incidence fell in both the control and intervention groups in both the landmark papers that informed the World Health Organization (WHO) decision to admit misoprostol to the 17th Essential Medicines List. This suggests factors other than misoprostol use are crucial in determining outcomes. Current evidence does not support misoprostol use in home and community settings in low- and middle-income countries for PPH prevention.

(See Enclosure 1 and Ref. 7)
Since the publication of our paper in 2012 there have been two other recent reviews of misoprostol including a Cochrane systematic review. The Cochrane systematic review ‘Prostaglandins for preventing postpartum haemorrhage’ (Enclosure 2) confirms our concerns about the quality of evidence and the impossibility of pooling. The review looked at 68 trials conducted in low-, middle- and high-income countries and the four community studies (cited above) conducted in low-income countries. They also stated that “all four recent trials have design and setting differences that make the summing up of their results difficult” (p.13). The review of the Guinea-Bissau trial (4) showed that almost half the women in the trial experienced higher than usual blood loss while the Gambia trial (3) was inadequately powered. The India 2006c trial (5) was deemed more applicable to community settings where the ‘expectant’ management of the third stage of labour is the norm (Enclosure 2, p.14). Although the results of this study were significant (RR 0.20; 95% CI 0.04 to 0.91, 2/812 versus 10/808), Cochrane reviewers do not discuss the weakening of the association by the observation of temporal trends in the intervention and control arms (suggesting effects from factors other than misoprostol) nor do they mention the lack of generalisability because the RCT excluded women with or at high risk of complications.

The most recent review by Hundley et al. (Enclosure 3) draws conclusions which do not match the results and the analysis because they misapplied SIGN GRADE criteria. We highlight these serious errors in our commentary which accompanies their paper (Enclosure 3).

11. Summary of comparative evidence on safety*:

N/A

• Estimate of total patient exposure to date
• Description of adverse effects/reactions
• Identification of variation in safety due to health systems and patient factors
• Summary of comparative safety against comparators

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

N/A

• range of costs of the proposed medicine
• comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality adjusted life year gained)

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Two different products containing misoprostol are registered with the US FDA, Arthrotec and Cytotec; neither of them have regulatory approval for prevention of post-partum haemorrhage or any other maternal health indication (US FDA website, accessed on January 7, 2013).
Four different products containing misoprostol have been authorized by the MHRA, Arthrotec, Cytotec, Medabon and Normulan. From these only Medabon, a combination of Mifepristone and Misoprostol, is approved for a maternal health indication - medical termination of a pregnancy (MHRA website, accessed on January 7, 2013).

Misoprostol for prevention and treatment of post-partum haemorrhage has been licensed in several developing countries (8). The evidence base of safety and efficacy used for these approvals has not been evaluated to date. In Uganda, the dossier submitted to the National Drug Authority provided evidence on toxicological, quality and stability tests; no pharmacological or clinical trials relevant to the safety and efficacy of misoprostol in management of post-partum haemorrhage were submitted (personal communication). Misoprostol has been added to the National Essential Medicines List of Uganda following the WHO decision.


N/A

15. Proposed (new/adapted) text for the WHO Model Formulary

We request the Committee delete the following clause: “, and for prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used” from the Section 22.1 Oxytocics from the current WHO Model List of Essential Medicines (17th list).

The adapted formulation of the relevant section:

Section 22.1 Oxytocics

Tablet: 200 micrograms.*
* For management of incomplete abortion and miscarriage.

Vaginal tablet: 25 micrograms.*
* Only for use for induction of labour where appropriate facilities are available.

Enclosures:

References:


