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The Secretary and Committee Members
Expert Committee on the Selection and Use of Essential Medicines
Medicine Access and Rational Use (MAR)
Department of Essential Medicines and Pharmaceutical Policies (EMP)
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland

29 November 2012

Dear Committee Members

We are writing to ask you to review and rescind the decision made by 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 of lack of evidence of efficacy.

In August, we published a review of the clinical studies conducted in community and home settings of low- and middle-income countries in the Journal of Royal Society of Medicine. This review covered all the community settings based clinical trials submitted to and considered by the Expert Committee.

Our study adds important new evidence to the debate, providing, for the first time, a detailed critical appraisal of the quality of six studies (including the four RCTs used by the WHO) with respect to their design, intervention and outcomes. Such a detailed analysis has not been undertaken previously. We show important limitations in all the studies, namely lack of blinding, different interventions and training of skilled attendants in the intervention and control arm, extensive exclusion criteria and temporal trends. These limitations and differences in study design preclude pooling of the evidence to obtain an overall safety and efficacy profile of misoprostol in the studied settings. The lack of generalisability of findings and clear evidence of efficacy negates the WHO decision to make a positive recommendation for the use of misoprostol in low-resource settings.

The Cochrane Systematic Review of *Prostaglandins for preventing postpartum haemorrhage* by Tunçalp et al. published in August 2012 confirms our concerns about the quality of evidence and the impossibility of pooling. Its conclusions and recommendations differ from ours, and their own discussion of the four RCTs, in that the authors appear to weakly endorse the WHO decision by stating: “Neither intramuscular prostaglandins nor misoprostol are preferable to conventional injectable uterotonics as part of the management of the third stage of labour especially for low-risk women; however, evidence has been building for the use of oral misoprostol to be effective and safe in areas with low access to facilities and skilled healthcare providers and future research on misoprostol use in the community should focus on implementation issues”. It should be noted that in contrast to our study the Cochrane authors

did not conduct an exhaustive appraisal of the trials and this is of concern where Cochrane Systematic reviews are considered the key source of evidence. We are aware that international NGOs are using WHO endorsement of misoprostol for PPH prevention and its addition to the EML and weak recommendations of the Cochrane Review to promote misoprostol distribution in low- and middle-income countries.

Finally Hundley et al. (2012) conducted a similar analysis and their findings were the same as ours. However their conclusion did not reflect the results and the analysis because they misapplied SIGN GRADE criteria. We highlight these serious errors in our commentary which accompanies their paper.

To summarise, our study shows that current available evidence does not support misoprostol use for the prevention of postpartum haemorrhage in pregnant women in community settings in the absence of skilled birth attendants, antenatal screening and good referral systems. This is of concern because misoprostol is now being used extensively as the drug of choice and in place of oxytocin in a number of low income countries, including Uganda and Nepal.

We are now formally requesting that the committee review the evidence and rescind the decision to place misoprostol for the prevention of PPH in pregnant women on the WHO EML. We would also ask that the WHO conduct a review of the networks, funding, conflicts of interest and motives of organisations promoting research into and the distribution of misoprostol in low- and middle-income countries, not least those who conducted and submitted the earlier reviews to the 17th and 18th Expert Committees.

We enclose our study and responses to our study by various authors and organisations. It is noteworthy that there has been no rebuttal of the science behind our analysis or our conclusion. Our responses are also attached.

Thank you for considering our application requesting deletion of misoprostol for prevention of postpartum haemorrhage from the WHO Essential Medicines List. Please do not hesitate to contact us would you need any further information.

Yours sincerely

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Encl.

- Chu CS, Brhlikova P, Pollock AM (2012) Rethinking WHO guidance: review of evidence for misoprostol use in the prevention of postpartum haemorrhage
- PH technical memo http://www.pathfinder.org/assets/Pathfinder-Technical-Memo-No-08-Misoprostol-for-PPH-Prevention-PDF.pdf
- FIGO statement http://www.cngof.asso.fr/D_TELE/FIGO_Statement_Misoprostol120831.pdf
- Quick comments by R Derman, NL Kerr, M Potts et al., and our quick response to R Derman published in the JRSM online http://jrsm.rsmjournals.com/content/105/8/336.abstract#responses
- Pollock, AM and Brhlikova, P (forthcoming in the JRSM) A Response to the Responses to 'Rethinking WHO guidance: review of evidence for misoprostol use in the prevention of postpartum haemorrhage' written by Derman, Kerr and Potts and published in JRSM and Pathfinder International *(not yet available)*
- BMJ 2012 'Questions raised over use of misoprostol to prevent postpartum haemorrhage in poor countries' http://www.bmj.com/content/345/bmj.e5715.full
- Response to Pathfinder International Technical Memo
- Hundley VA et al (2012) with commentary by Pollock AM, Brhlikova P, McGettigan P (2012) Commentary on 'Should oral misoprostol be used to prevent postpartum haemorrhage in home-birth settings in low-resource countries? A systematic review of the evidence'