



FIAPAC Statement on the use of Misoprostol in Women's Health Care

www.fiapac.org. October 2011

The prostaglandin E₁ analogue is approved for the prevention and treatment of gastro-duodenal ulcers for patients being treated with non-steroidal anti-inflammatory drugs (NSAIDs) - see Table I. It has been on the market since 1985 and is approved in more than 90 countries under the brand name of Cytotec[®].

Misoprostol has several advantages over other prostaglandins on the market. Being an E₁ analogue, it has no effect on the bronchii and the blood vessels. It can be stored at room temperature for a long time provided the aluminium blister is not opened. The 200 microgram tablets are approved for oral use, but there are numerous publications showing the effectiveness of other routes of administration such as vaginal, sublingual, buccal and rectal. The only relevant side effects in clinical practice are gastrointestinal (diarrhoea, nausea, vomiting, oral numbness), skin rash and fever, which are dose and route dependent and self-limiting.

Table I: Fact sheet on Misoprostol	
Brand name	Cytotec®
Chemical name	Misoprostol
Producer/patent holder	Pfizer, US (formerly Searle)
First marketed	1985 (Mexico)
Group	Prostaglandin E ₁ analogue
Available as	Tablets, oral, 200 microgram (100 and 50 (vaginal) microgram tablets are available in some countries)
Approved indication	Prevention and treatment of gastro-duodenal ulcers for patients being treated with NSAIDs
Pharmacokinetics after oral administration	Absorption: rapid T _{max} : 12 ± 3 minutes Terminal half-life: 20-40 minutes. First uterine contractions after 15-20 min Elimination: 80% via urine

Today, there is an abundant amount of literature on the safe and effective use of misoprostol for different indications and the number of publications and amount of evidence continues to increase (see www.misoprostol.org).

Based on the available evidence, even the British Medical Association and Royal Pharmaceutical Society recommend in the British National Formulary the use of misoprostol for unlicensed indications (Table II); a truly rare event.

All evidence based guidelines recommend the use of misoprostol in various routes of administration: oral, vaginal, sublingual or buccal (5,6,10). (Table III and IV)

Misoprostol is present in the WHO essential medicines list for induction of labour, medical abortion together with mifepristone where abortion is legal, and for incomplete abortion. Furthermore it is approved in some countries for post-partum haemorrhage.

Table II

Citation from the British National Formulary

No. 61, March 2011

Pages 486, 488 and 489

Misoprostol:**Induction of abortion:**

Misoprostol is given by mouth or by vaginal administration to induce medical abortion (unlicensed indication).

Induction and augmentation of labour:

Misoprostol is given orally or vaginally for the induction of labour (unlicensed indication).

Table III: Citation from the British RCOG evidence based guideline (5)

A

42.* Misoprostol (a prostaglandin E₁ analogue) is a cost-effective alternative for all abortion procedures for which the E₁ analogue gemeprost is conventionally used (that is, early medical abortion, cervical priming, mid-trimester medical abortion).

Table IV: Citation from the recent French evidence based guidelines

Les études évaluant l'efficacité du misoprostol, après 200 mg de mifépristone, selon sa voie d'administration sont en faveur d'une efficacité de la voie sublinguale (hors AMM) et buccale (hors AMM) comparable à celle de la voie vaginale (hors AMM), et supérieure celle de la voie orale (hors AMM au-delà de 7 SA) jusqu'à 9 SA.

Recommandations de bonne pratique - Interruption volontaire de grossesse par méthode médicamenteuse, 2010, Haute Autorité de santé, Paris

The recommendations on dose and route of administration when used for medical abortion in the first and second trimester and for cervical priming prior to surgical abortion is given in the WHO safe abortion guidance as well as in the Royal College clinical practice guidelines, both of which are currently being updated. Furthermore FIGO has issued guidelines on the use of misoprostol in Obstetrics and Gynaecology which are available at www.misoprostol.org (Table V) (9)

In general the vaginal or sublingual application is more effective than the oral route and associated with lower incidence of side effects.

Table V: Indications and regimens for use of misoprostol in obstetrics and gynaecology. All dosages based on 200 microgram tablets. (9)		
Indication	Dosage	Notes
Induction of labour for live baby (>28 weeks)	1/4 tab per vaginam 6 hrly	Very effective. Now first line in many European and US centres. Beware of hyperstimulation. Should not be used if previous Caesarean section.
Induction of labour for intrauterine fetal death (>28 weeks)	1/2 – 1 tab sublingual/pv 12hrly	Good. First line treatment in many centres in Europe and US. Usually used following mifepristone, but works without.
Missed abortion (12-28 weeks)	2 tabs sublingual/oral/pv 4 hrly	More effective than oxytocin. Best used following mifepristone priming.
Missed abortion (0-12 weeks)	2 tabs sublingual/oral/pv 4 hrly or 4 tabs pv 24 hrly	95% effective.
Incomplete abortion (0-12 weeks)	3 tabs oral	Good – now a standard option in Europe. >95% effective.
Postpartum haemorrhage - prevention - treatment - during C-section	- 3 tabs orally - 5 tabs per rectum/3 tab sublingual - 2 tabs sublingual	Prophylactic not as effective as injectable oxytocics, but useful as treatment option.
Cervical ripening prior to uterine instrumentation	2 tabs oral/ pv stat 2hours before procedure	Reduces perforation and failure rates.

Off-label use of medicines

A drug licence alone is not the appropriate determinant of whether a drug is effective for any given indication. The system of drug licensing was set up to regulate the pharmaceutical industry and not the medical profession, and its advice should always be seen in this context. Furthermore, the current licensing system is inadequate in a situation where the patent holder decides not to apply for an indication as is the case for misoprostol. (7)

Conclusions

Misoprostol has huge potential in obstetric and gynaecological practice and the low rate of side effects. Unfortunately its crucial beneficial role in women's health care are currently not sufficiently acknowledged. The lack of approved indications for misoprostol in Obstetrics & Gynaecology in Europe should not deter health professionals from using it for indications where there is sufficient evidence for its safe and effective use.

A dedicated misoprostol product approved for several reproductive health indications is available in France under the name of Gymiso[®].

References

1. Misoprostol for Women's Health: A Review, Blanchard et al., Obstetrics & Gynecology, February 2002, Vol 99, No 2: 316-32
2. Managing Complications in Pregnancy and Childbirth, World Health Organization, 2000, WHO/RHR/00.7; IMPAC, P25
3. Hill K et al. Estimates of maternal mortality for 1995, Bulletin of the World Health Organization, 2001, 79:182-93, http://www.who.int/reproductive-health/publications/RHR_01_9_maternal_mortality_estimates/statement_on_maternal_mortality_estimates.en.html
4. Demographic and Health Survey Uganda 2000-2001, Uganda National Bureau Of Statistics, Entebbe, Uganda, December 2001
5. Royal College of Obstetricians and Gynaecologists (RCOG). The care of women requesting induced abortion. Evidence-based clinical guideline no. 7. 2004 [London].
6. WHO safe abortion guidance, Geneva 2003
7. Weeks AD, Fiala C, Safar P. Misoprostol and the debate over offlabel drug use. [BJOG 2000;112:269-72.](#)
8. Fiala C, Gemzell-Danielsson K, Review of medical abortion using mifepristone in combination with a prostaglandin analogue, [Contraception 2006 \(74\):66-86](#)
9. [Misoprostol for reproductive health, IJGO, 2007, Vol 99 \(supplement 2\), a special issue with articles covering different aspects published by authors from an expert group](#)
10. [Recommandations de bonne pratique - Interruption volontaire de grossesse par méthode médicamenteuse, 2010, Haute Autorité de santé, Paris](#)