**MISOPROSTOL, (Low Dose for labour induction at term)**

1. **Summary statement of the proposal for inclusion**

Misoprostol, a synthetic prostaglandin E1 analogue, is proposed for inclusion in WHO Model List of Essential Medicines for labour induction at term, to be used in low dose (25mcg – 50 mcg).

Prostaglandin analogues are used in labour induction and augmentation.\(^1,2\) Labour induction is an intervention that artificially initiates uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby, and is to be considered when the risks of continuing pregnancy are outweighed the risks of terminating it.

Labour induction is a cornerstone treatment for a broad range of conditions – some of which are common, for which a prompt delivery reduces maternal or neonatal morbidity and mortality. Examples of frequent conditions are post-term pregnancy, pregnancy induced hypertension, pre-eclampsia and eclampsia, premature rupture of membranes, intrauterine fetal growth retardation chorioamnionitis, fetal death, and maternal diabetes. Other less common but severe conditions include chronic renal disease, antiphospholipid syndrome, thromboembolism, severe dermatosis and previous stillbirth. The above lists are not exhaustive. When fetal maturity is guaranteed, psychosocial or logistical factors may turn into indications for labour induction.

WHO guidelines address induction of labour with misoprostol in:
- selected populations such a women with pre-eclampsia or eclampsia and with an unfavourable cervix if a caesarean is unsafe.\(^3\)
- women who have had in-utero fetal death who have decreasing platelets and no spontaneous labour.\(^3\)

WHO guidelines list misoprostol along dinoprostone and carboprost – other prostaglandin analogues, as oxytocics.\(^4\) Unlike most prostaglandin analogues registered for cervical ripening and labour induction, misoprostol is inexpensive, easily stored at room temperature and has few systemic side effects.\(^5\)

Studies on the use of misoprostol for induction of labour [unlicensed indication] have used tablets administered by different routes including sublingual, vaginal, rectal and by mouth. Misoprostol and other prostaglandin analogues are also used to treat and prevent postpartum haemorrhage, to prevent NSAID induced ulcers and their complications, and for termination of pregnancy.\(^1\)

2. **Name of the focal point in WHO submitting or supporting the application**

- Dr. Metin Gülmezoglu UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in
3. Name of the organization(s) consulted and/or supporting the application

- **BMJ Knowledge** (Dr. Luis Gabriel Cuervo)

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

- Misoprostol

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

- Prostaglandin analogues

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

   It is difficult to obtain global data of labour inductions or labour inductions at term, but labour induction is frequently used. It is estimated that it is used in over 10% of deliveries, and in hospitals, inductions may be used in about 5% to 30% of deliveries, depending on the setting, but the mode of labour induction may be in the figures of 20%-25% of deliveries amongst referral hospitals; there are great variations between settings.\(^\text{(6−14)}\)

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

   WHO guidelines recommends using misoprostol for cervical (in labour induction) only in highly selected situations such as: (1) severe pre-eclampsia or eclampsia when the cervix is unfavourable and safe caesarean section is not immediately available or the baby is too premature to survive; (2) fetal death in-utero if the woman has not gone into spontaneous labour after 4 weeks and platelets are decreasing.

   The recommended dose in these WHO guidelines is 25 micrograms placed in the posterior fornix of the vagina, and this dose should be repeated after 6 hours if required. If there is no response after two doses of 25 mcg, the dose should be than increased to 50 mcg every 6 hours. The dose should not exceed 50 mcg at a time or a total of four doses (200 mcg). Oxytocin should not be used within 8 hours of using misoprostol. Uterine contractions and fetal heart rate should be monitored.\(^\text{(3)}\)
8. 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)

  A search of the Cochrane Library (issue 1, 2005) was done using the version available from the British National Health Library in January 2005. Additional searches to identify background papers and recent RCTs were done using the Clinical Queries of PubMed in January 2005.

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

Does it work? Comparisons against placebo

Vaginal misoprostol versus placebo

A Cochrane review (Search date February 2004, 5 controlled trials, 339 women) compared the effects of vaginal misoprostol with placebo. It found that in women with unfavourable cervix and intact membranes, misoprostol reduced the risk of failure to deliver within 24 hours, but increased uterine hyperstimulation. The one RCT identified by the review included only women with unfavourable cervix and intact membranes, and compared misoprostol 100 mcg crushed and mixed with 5 ml hydroxymethyl cellulose gel into the posterior vaginal fornix, with gel alone. The review was underpowered to rule out other clinically important outcomes particularly amongst subgroups including women with ruptured membranes. It also found that lower doses of misoprostol were associated with more need of oxytocin augmentation and less uterine hyperstimulation. (5)

Oral misoprostol versus placebo

A Cochrane review (Search date December 2000, 1RCT, 80 women with premature rupture of membranes) compared the effects of oral misoprostol with placebo. The RCT was underpowered to detect clinically important differences (showing broad non-significant confidence intervals) except for a significant reduction in the need for oxytocin augmentation (5/39 [13%] with misoprostol v 21/41 [51%] with placebo; RR 0.25 95% CI 0.10 to 0.60). (15)

Is it a good option? Comparisons against other treatments:

Versus prostaglandin analogues: One Cochrane review (Search date February 2004, 13 RCTs, 2906 women) assessed the effects of vaginal misoprostol versus vaginal prostaglandin analogues (dinoprostone in all RCTs). Compared with vaginal dinoprostone, misoprostol reduced risk of not achieving delivery within 24 hours but it also increased uterine hyperstimulation with and without fetal heart rate changes (Table 1). Misoprostol was also associated with a slight reduction in the use of epidural analgesia (9% reduction). No significant differences were found in serious neonatal morbidity or perinatal mortality, uterine rupture, Apgar <7 at 5 minutes, admission to neonatal intensive care, or postpartum haemorrhage.

Versus oxytocin: when compared with oxytocin, misoprostol had a
borderline statistical reduction of failure to achieve vaginal delivery (5 RCTs, 540 women; RR 0.66, 95% CI 0.44 to 1.00). This reduction was more clearly noticed among women with variable or undefined cervix (2 RCTs, 278 women; RR 0.46, 95% CI 0.30 to 0.68). Misoprostol also increased uterine hyperstimulation with fetal heart rate changes (9 RCTs, 1271 women; RR 2.22, 95% CI 1.77 to 2.79). Additional data is available from Table 1.\(^5\)

How should it be better used? Comparisons of different routes and doses:

Different doses of misoprostol: A Cochrane review (Search date February 2004, 13 RCTs, 2138 women) compared the effects of different doses of vaginal misoprostol.\(^5\) The compared doses were: 12.5 versus 25 mcg 6-hourly (1 RCT); 25 v 50 mcg 3 to 6-hourly (7 RCTs); 35 v 50 mcg 4.5-hourly (1 RCT); and 50 v 100 mcg 4 to 6-hourly (4 RCTs). The lower dosage regimens did not show more failures to achieve delivery within 24 hours, but there was increased use of oxytocin (12 RCTs, RR 1.23, 95% CI 1.08 to 1.40). This effect was due to the trials with a lower range of doses, and was not seen in the trials in which the lower dosage was 50 mcg.\(^5\) Based on the analysis, the Cochrane reviewers recommend a starting dose of 25 mcg every four hours.

Oral versus vaginal misoprostol A Cochrane review (Search date December 2000, 7 RCTs, 1278 women) compared swallowed misoprostol with vaginal misoprostol. It found oral misoprostol to be less effective as it increased the chances of failure to achieve vaginal delivery within 24 hours (4 RCTs; 50% v 40%; RR 1.27, 95% CI 1.09 to 1.47), and this was clear with the 50 mcg dose (Table 2). However, oral misoprostol was associated with a lower risk of caesarean section. No significant differences were found for uterine hyperstimulation with fetal heart rate changes and no severe neonatal or maternal morbidity was reported.\(^15\) A more recent Cochrane review (Search date December 2003) assessed the effects of swallowed and sublingual administration of misoprostol for induction of labour.\(^16\) It found insufficient evidence to establish if misoprostol by mouth is more effective swallowed or sublingual.

### Summary of available estimates of comparative effectiveness

<table>
<thead>
<tr>
<th>Versus placebo in women with intact membranes and unfavourable cervix</th>
<th>RCTs</th>
<th>AR [%]</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery not achieved within 24 hours</td>
<td>50%</td>
<td>18/32 [25%]</td>
<td>0.36</td>
<td>0.19 to 0.68</td>
</tr>
<tr>
<td>Uterine hyperstimulation + FHR* changes</td>
<td>3</td>
<td>5/113 [4%]</td>
<td>2.31</td>
<td>0.52 to 10.16</td>
</tr>
<tr>
<td>Uterine hyperstimulation without FHR* changes</td>
<td>3</td>
<td>14/83 [17%]</td>
<td>10.11</td>
<td>1.91 to 53.60</td>
</tr>
</tbody>
</table>

Table 2. Oral versus vaginal 50 mcg misoprostol (15)

<table>
<thead>
<tr>
<th>Oral versus vaginal misoprostol</th>
<th>RCTs</th>
<th>AR [%] Oral</th>
<th>AR [%] Vaginal</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery not achieved within 24 hours</td>
<td>2</td>
<td>150/232 [65%]</td>
<td>89/233 [38%]</td>
<td>1.69</td>
<td>1.40 to 2.04</td>
</tr>
</tbody>
</table>

9. Summary of comparative evidence on safety:

- **Estimate of total patient exposure to date**

It is difficult to estimate how many women have been exposed to misoprostol, and specifically during labour induction or labour induction at term. Surrogate indicators suggest that misoprostol is being widely used throughout the world. For example, misoprostol is recommended in numerous published reports of trials, clinical guidelines and textbooks addressing induction of labour and induction of labour at term.
• **Description of adverse effects/reactions**

**In women in labour:** Uterine hyperstimulation was the most frequently observed adverse effect documented in RCTs assessing the effects of misoprostol in labour induction (Table 1). This increase in hyperstimulation was found when misoprostol was compared with placebo or dinoprostone.\(^{(5)}\) Uterine rupture, perinatal death and maternal death were not assessed systematically in RCTs. Furthermore, in the few RCTs that did collect this data systematically the incidence was too low to reach any additional conclusions or estimate an incidence from the data provided by those small RCTs.

**In other populations:** Other adverse effects are uncommon and usually dose related; amongst them, diarrhoea which is usually mild. In people with Chron’s ileocolitis incapacitating diarrhoea attributed to misoprostol and requiring treatment withdrawal affected 8/2003 [0.4%] people. Other potential gastrointestinal adverse effects include abdominal pain, dyspepsia, flatulence and, nausea and vomiting. Skin rashes headache and dizziness have also been reported. Hypotension is rarely seen at recommended doses. Prostaglandin analogues have been used to cause termination of pregnancy and to induce cervical changes even at the early stages of pregnancy. Anecdotal reports and one small controlled trial suggest that use of misoprostol during first trimester of pregnancy may cause congenital malformations.\(^{(1)}\)

• **Identification of variation in safety due to health systems and patient factors**

Misoprostol tablets are usually available in 200 mcg presentation. The administration of lower doses thus involves fragmenting tablets which makes it difficult to guarantee that a uniform dose is being delivered.\(^{(17)}\)

A Cochrane review (Search date February 2004, 1 RCT, 467 participants) assessed the effects of misoprostol gel compared with misoprostol tablets. It found that misoprostol gel halved uterine hyperstimulation, but increased the use of oxytocin and epidural analgesia.\(^{(5)}\) Misoprostol gel is not widely available.

• **Summary of comparative safety against comparators**

See above

10. **Summary of available data on comparative cost\(^1\) and cost-effectiveness within the pharmacological class or therapeutic group:**

• **Range of costs of the proposed medicine**

Misoprostol is considerably cheaper than both intravaginal and intracervical dinoprostone (a prostaglandin analogue, licensed for this indication in UK). The Royal College of Physicians found that taking as a reference the recommended regimen of vaginal dinoprostone tablet, that relative costs compared with vaginal misoprostol would be £0.18 per 200 mcg tablet of misoprostol versus £8.13 for a 3 mg dinoprostone tablet. Compared with dinoprostone, misoprostol reduces the incidence of operative deliveries, therefore a further indirect cost savings would be expected.\(^{(17)}\)
Misoprostol is included in the British National Formulary in 200 mcg scored tablets available in packets of 60 tablets (£10.03), or 140 tablets (£23.40); hence the price per 200 mcg tablet in the UK is £0.167. Dinoprostone, a prostaglandin analogue licensed for labour induction, is available in 5 mg pessaries (£43.44 per pessary), solutions for intravenous and extra-amniotic use (seldom used nowadays) and vaginal 3 mg tablets sold in 8 tablet packs (£78.05 per pack, equivalent to £9.76 per tablet); A 5u injection of oxytocin costs £1.23, but this does not include the additional direct costs of the necessary infusion system.\(^{(18)}\)

In the US a dose of misoprostol would cost under one US dollar, whilst dinoprostone costs over $150 USD.\(^{(19)}\)

An RCT assessing active management of labour in Colombia found that the average direct costs per patient (drug plus necessary equipment) for the administration of three different uterotonics were: misoprostol COL $500 (USD 0.21; £0.11); Oxytocin COL $8000 (USD 3.37; £1.78); methylergometrine COL 2000 (USD $0.84; £0.45).\(^{(20)}\)

- **comparative cost-effectiveness presented as range of cost per routine outcome**

Further data is needed about the theoretical risks of misoprostol. Therefore, until these are available there will remain considerable uncertainty about its overall cost effectiveness.

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

Misoprostol has been registered for cervical ripening and labour induction in Brazil since June 2001.\(^{†}\) It is a controlled drug to be delivered only in hospital based obstetric centres with good conditions to manage adverse effects.\(^‡\) The recommended dose a 25 mcg intravaginal tablets to be repeated every 4 to 6 hours. [Personal communication: M. Gulmezoglu; Lenita Wannmacher. 2005]  
\(^{‡}\) (Portaria nº 344, de 12 de Maio de 1998, Aprova o Regulamento Técnico sobre substâncias e medicamentos sujeitos a controle especial)


- Misoprostol (BAN, USAN, rINN)

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

1. Index “labour, induction”; “prostaglandin analogues”; “misoprostol”; “prostaglandin E1analogue”.
2. Add Misoprostol under section “22.1 Drugs used in obstetrics”
Misoprostol
Misoprostol is a synthetic analogue of alprostadil (prostaglandin E1) which has been used to treat benign gastric and duodenal ulcerations, particularly when associated to the use of NSAIDs. Misoprostol has a uterotonic effect, therefore it has been used to induce labour in a range of indications including intrauterine death, prevent and treat postpartum haemorrhage, and terminate pregnancy. Misoprostol scored tablets 200 micrograms.

**Uses:** Labour induction at term.

**Contraindications:** Fetal distress; Cephalopelvic disproportion; Contraindications for vaginal delivery; Uterine tachysystole; uterine hypertonus or uterine hyperstimulation; Oblique or traverse lie; Severe placenta previa; severe hypotension; hypersensitivity to prostaglandins. Do not administer misoprostol when continuation of pregnancy is desirable; misoprostol may induce termination of pregnancy at every gestational age.

**Precautions:** uncertainty about gestational age, prior caesarean section, previous uterine surgery or uterine rupture, concomitant use of oxytocin; if induction is to be continued with oxytocin, it is recommended to leave 4 hours after the last dose of misoprostol and the initiation of oxytocin. Oral administration with food reduces the rate but not the extent of absorption. Misuse of misoprostol during first trimester of pregnancy has been associated with congenital malformations. Misoprostol can induce uterine hyperstimulation with and without fetal heart rate changes. Multiple pregnancies. Fetal and maternal monitoring is recommended in any labour induction.

**Interactions:** its concomitant use with other uterotonics may lead to hyperstimulation and increase the risk of uterine rupture and fetal distress.

**Dosage:** Misoprostol tablets 25 – 50 mcg inserted into the posterior vaginal fornix every 4 to 6 hours until 3 contractions per 10 minutes is reached, or a cervical score of ≥8, or cervix dilates ≥3cm. Recommended not to exceed 6 doses.

**Adverse effects:** uterine hyperstimulation, is the most frequent adverse effect; it may be accompanied of fetal heart rate changes in about 5% to 10% of patients. Uterine rupture, particularly in women with scarred uterus. Fetal distress. Other adverse effects are uncommon in pregnant women at the recommended dose and include diarrhoea, headaches, abdominal discomfort, dyspepsia, nausea and vomiting, skin rashes, headache, dizziness.

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1 Information on cost and cost-effectiveness should preferably refer to average generic world market prices as listed in the International Drug Price Indicator Guide, an essential medicines pricing service provided by WHO and maintained by Management Sciences for Health. If this information is not available, other international sources, such as the WHO, UNICEF and Médecins sans Frontières price information service, can be used. All cost analyses should specify the source of the price information.
Reference List


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