Induction of labour in late intrauterine fetal death: vaginal misoprostol (after oral mifepristone)

Evidence summary
Published: 30 April 2013
nice.org.uk/guidance/esuom11

Key points from the evidence
The content of this evidence summary was up-to-date in April 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary
Off-label use of lower doses of vaginal misoprostol (after oral mifepristone) for the induction of labour in women with late intrauterine fetal death (IUFD) is supported by 2 small case series that provide limited evidence of similar effectiveness compared with higher doses. While there is some suggestion of improved tolerability with the lower dose regimen, in both case series, the analysis of serious adverse effects is limited by the small numbers in the studies.

Regulatory status: off-label
Effectiveness

- 2 case series comparing lower doses of vaginal misoprostol with higher doses
- Limited evidence of similar effectiveness
- More evidence is needed to confirm these findings

Safety

- In 2 case series, the numbers of serious side effects were small and similar between the groups

Patient factors

- Limited evidence of improved tolerability with lower dose regimens
- Further evidence is required to confirm these findings

Cost

- Approximately £10 for a pack of 60 misoprostol 200 microgram tablets

Key points

Misoprostol is a synthetic prostaglandin E₁ analogue that softens the cervix and can stimulate uterine contractions. It is not currently licensed in the UK for the induction of labour in women with late intrauterine fetal death (IUFD); use for this indication is off-label.

Induction of labour (NICE clinical guideline 70) recommends that, if a woman who has had a late IUFD chooses to proceed with induction of labour, mifepristone should be used, followed by vaginal prostaglandin E₂ or misoprostol.

An update to the Royal College of Obstetricians and Gynaecologists' (RCOG) guideline on the management of late IUFD and stillbirth noted that some hospitals in the UK were using larger doses of misoprostol than recommended, potentially leading to an increased risk of adverse effects.

This evidence summary describes the risks and benefits of vaginal misoprostol, when used after oral mifepristone, as in the NICE guidance on the induction of labour in late IUFD. It focusses particularly on the dose of vaginal misoprostol.

No randomised controlled trials were identified that met the inclusion criteria. Two case series were found that compared a low-dose misoprostol treatment regimen (administered vaginally following oral mifepristone as recommended by NICE) with a higher dose regimen (in 1 study...
administered orally and vaginally after mifepristone, and in 1 study administered vaginally without pre-treatment with mifepristone) for induction of labour after late IUFD, using a historical control group.

The results of the first case series (Fairley et al. 2005, n=47) suggest that oral mifepristone followed by low doses of vaginal misoprostol (mean total dose 167 micrograms) is similarly effective to oral mifepristone followed by a combination of vaginal and oral misoprostol (mean total dose 828 micrograms). However, the statistical significance of any differences between the groups was not reported.

The second case series (Vayrynen et al. 2007, n=130) suggests that oral mifepristone followed by a low dose of vaginal misoprostol (median total dose 100 micrograms) is similarly effective to a higher dose of vaginal misoprostol used on its own without mifepristone (median total dose 200 micrograms).

In both case series, the analysis of serious adverse effects is limited by the small numbers in the studies.

These 2 case series suggest that low dose vaginal misoprostol following mifepristone is effective at inducing labour in late IUFD. Further research is needed to evaluate the safety and efficacy of different dosages of vaginal misoprostol used for this indication.

**About this evidence summary**

‘Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.
Overview for healthcare professionals

Induction of labour (NICE clinical guideline 70) recommends that, if a woman who has had an intrauterine fetal death (IUFD) chooses to proceed with induction of labour, oral mifepristone should be used, followed by vaginal prostaglandin E₂ or vaginal misoprostol (prostaglandin E₁, off-label). This evidence summary describes the risks and benefits of vaginal misoprostol, when used after oral mifepristone according to NICE guidance.

The Royal College of Obstetricians and Gynaecologists' (RCOG) guideline on the management of late IUFD (after 24 completed weeks of pregnancy) and stillbirth advises that the dose of misoprostol should be adjusted according to gestational age (100 micrograms 6-hourly before 26 weeks; 25 to 50 micrograms 4-hourly at 27 weeks or more). An update to the RCOG guideline in July 2011 noted that some hospitals in the UK were using larger doses of misoprostol than recommended in the 2010 guideline, potentially leading to an increased risk of adverse events. This evidence summary focusses particularly on the dose of misoprostol.

Regulatory status of misoprostol

Misoprostol is not currently licensed in the UK for the induction of labour in women with late IUFD.

Misoprostol 200 microgram oral tablets (Cytotec, Pharmacia Limited) are licensed in the UK for treating duodenal and gastric ulcers and preventing non-steroidal anti-inflammatory drug-induced ulcers in adults.

Medabon (Sun Pharmaceutical Industries Europe) is a combination pack containing 1 oral mifepristone 200 mg tablet and 4 vaginal misoprostol 200 microgram tablets. It received UK marketing authorisation in May 2012 for the termination of intrauterine pregnancy of up to 63 days of amenorrhoea.

MisoOne (Exelgyn) contains 400 micrograms of misoprostol for oral administration. In January 2013 it was licensed in the UK for the termination of intrauterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea.

The use of any of these products for the induction of labour in late IUFD is off-label. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using misoprostol outside its authorised indications.
Evidence statements

No randomised controlled trials were identified that compared the risks and benefits of vaginal misoprostol, when used after oral mifepristone according to NICE guidance on the induction of labour in late IUFD. This evidence summary includes 2 case series that compared a low-dose misoprostol treatment regimen with a higher dose regimen for induction of labour after late IUFD, using a historical control group.

- The results of the first case series (Fairley et al. 2005, n=47) suggest that oral mifepristone followed by low doses of vaginal misoprostol (mean total dose 167 micrograms) is similarly effective to oral mifepristone followed by a combination of vaginal and oral misoprostol (mean total dose 828 micrograms). However, the statistical significance of any differences between the groups was not reported.

- The results of the second case series (Vayrynen et al. 2007, n=130) suggest that oral mifepristone followed by a low dose of vaginal misoprostol (median total dose 100 micrograms) is similarly effective to a higher dose of vaginal misoprostol used on its own without mifepristone (median total dose 200 micrograms).

- In both case series, the analysis of serious adverse effects is limited by the small numbers in the studies.

- A Cochrane review on induction of labour in the second and third trimester for fetal anomaly or after IUFD states that vaginal misoprostol is as effective as other agents with a lower incidence of common gastrointestinal adverse effects, but there are insufficient data to assess the occurrence of rare but potentially life-threatening complications for the woman, including uterine rupture.

- Although the summary of product characteristics for the licensed misoprostol preparation does not apply to this indication or route of administration, prescribers should take the listed adverse effects into account when considering safety for the induction of labour in women after late IUFD.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the Evidence review section.

This evidence summary includes 2 case series in which the groups of women being examined were studied over different time periods after a change in practice in the study hospitals. The aim of both
case series was to compare the effects of 2 different regimens of misoprostol treatment for induction of labour after late IUFD.

Efficacy

*Mifepristone plus vaginal and oral misoprostol compared with mifepristone plus vaginal misoprostol*

The UK case series by Fairley et al. (2005) compared low-dose vaginal misoprostol (50 micrograms 3-hourly) with a higher dose administered both vaginally and orally (400 micrograms 4-hourly) in 47 women with late IUFD (24 weeks gestation or later). All women took mifepristone 200 mg orally before misoprostol was administered. The group that used the vaginal and oral misoprostol combination (n=29) was treated between February 1998 and December 2001, whereas the group that used vaginal misoprostol alone (n=18) was treated between March 2002 and May 2003. Information was gathered prospectively. Outcomes included the time from administration of the first dose of misoprostol (induction) to fetal delivery, analgesic requirements and adverse events. See table 1 for more details.

Women in the combined vaginal and oral administration group received a higher mean total dose of misoprostol (828 micrograms) compared with the vaginal administration only group (167 micrograms). The median induction to fetal delivery interval was 7 hours (range 1.5 to 29.5) in the combined vaginal and oral administration group and 10.2 hours (range 1.5 to 20.0) in the vaginal administration only group. The statistical significance of the difference in induction to delivery time was not reported.

Although women who received a higher dose of misoprostol delivered 3 hours faster on average, this study suggests that low-dose misoprostol (mean 167 micrograms) administered vaginally is effective for the induction of labour after IUFD at 24 weeks gestation or later.

*Misoprostol alone compared with mifepristone plus misoprostol*

The Finnish case series by Vayrynen et al. (2007) compared the use of vaginal misoprostol alone (between 1997 and 2001) with oral mifepristone 200 mg followed by vaginal misoprostol (between 2001 and 2005) in 130 women with IUFD (22 weeks gestation or later). Single 4-hourly doses of 25 to 400 micrograms (median 100 micrograms) were used in the vaginal misoprostol alone group (n=82) compared with 25 micrograms in the combination treatment group (n=48). Study outcomes included induction to delivery time, need for oxytocin or analgesia, and adverse events. See table 2 for more details.
The median total dose of misoprostol was significantly lower in the combination mifepristone and misoprostol treatment group compared with the misoprostol only group (100 micrograms compared with 200 micrograms, \(p=0.0028\)). However, the median number of doses needed was higher in the combination treatment group compared with the misoprostol only group (3 compared with 2, \(p=0.0019\)).

The study found no significant difference between the groups in the induction to delivery interval. The median induction to fetal delivery interval was 12.8 hours (range 3.2 to 12.9) in the combined mifepristone and misoprostol group and 13.3 hours (range 2.1 to 97.3) in the vaginal misoprostol only group.

The results of this study suggest that, when used after mifepristone according to NICE guidance, low-dose misoprostol (median 100 micrograms) is effective for the induction of labour after IUFD at 22 weeks gestation or later.

**Table 1 Summary of Fairley et al. (2005)**

<table>
<thead>
<tr>
<th>Dosage and route of administration</th>
<th>Combined vaginal and oral</th>
<th>Vaginal only</th>
<th>Comment and analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg mifepristone + 400 micrograms vaginal misoprostol + up to 4 doses of 400 micrograms oral misoprostol 4-hourly</td>
<td>200 mg mifepristone + 50 micrograms vaginal misoprostol + up to 4 doses of 50 micrograms vaginal misoprostol 3-hourly</td>
<td></td>
</tr>
<tr>
<td>Group allocation</td>
<td>n=29</td>
<td>n=18</td>
<td></td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>31 (5.4)</td>
<td>31 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Median gestation: weeks (range)</td>
<td>28 (24 to 40)</td>
<td>31 (24 to 41)</td>
<td></td>
</tr>
<tr>
<td>Previous C-section (%)</td>
<td>3 (10%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
</tbody>
</table>
### Induction of labour in late intrauterine fetal death: vaginal misoprostol (after oral mifepristone) (ESUOM11)

| Mean total dose of misoprostol: micrograms (range) | 828 (400 to 1000) | 167 (50 to 250) | Difference in mean dose: 661 micrograms

**Statistical significance not reported**

| Efficacy | Median time from first dose of misoprostol to delivery: hours (range) | 7 (1.5 to 29.5) | 10.2 (1.5 to 20.0) | Difference in median times: 3.2 hours

**Statistical significance not reported**

| Analgesia requirements | Parenteral opiates (controlled morphine infusion; intramuscular diamorphine) | 69% (20 women) Morphine: 14% (4 women) Diamorphine: 55% (16 women) | 78% (14 women) Morphine: 0 (0 women) Diamorphine: 78% (14 women) | Statistical significance not reported

| Requested epidural analgesia | 14% (4 women) | 6% (1 woman) | Statistical significance not reported

| Oral analgesia | Not reported | 17% (3 women) | 5 women (17%) from the combined vaginal and oral group were reported as receiving oral or no analgesia; numbers receiving oral analgesia not reported

### Safety

<p>| Maternal death | None reported | None reported |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Misoprostol only</th>
<th>Mifepristone plus misoprostol</th>
<th>Comment and analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal adverse events</td>
<td>48%</td>
<td>35%</td>
<td>Numbers of women not reported. Statistical significance not reported</td>
</tr>
<tr>
<td>Postpartum haemorrhage &gt;1000 ml needing blood transfusion</td>
<td>10% (3 women)</td>
<td>11% (2 women)</td>
<td>In the combined vaginal and oral group there was an additional case of postpartum haemorrhage &gt;1000 ml that did not need blood transfusion Statistical significance not reported</td>
</tr>
<tr>
<td>Manual removal of placenta</td>
<td>14% (4 women)</td>
<td>6% (1 woman)</td>
<td>Statistical significance not reported</td>
</tr>
</tbody>
</table>

Abbreviations: C-section, caesarean section; SD, standard deviation.

**Table 2 Summary of Vayrynen et al. (2007)**

<table>
<thead>
<tr>
<th></th>
<th>Misoprostol only</th>
<th>Mifepristone plus misoprostol</th>
<th>Comment and analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group allocation</strong></td>
<td>n=82</td>
<td>n=48</td>
<td>Labour was initiated in 2 women in the mifepristone plus misoprostol group by mifepristone only</td>
</tr>
<tr>
<td><strong>Mean age in years (range)</strong></td>
<td>30 (17 to 44)</td>
<td>32 (21 to 42)</td>
<td>p=0.088</td>
</tr>
<tr>
<td><strong>Median gestation: weeks + days (range)</strong></td>
<td>30+4 (21+5 to 40+3)</td>
<td>32+2 (22+1 to 41+0)</td>
<td>Not significant, p-value not reported</td>
</tr>
<tr>
<td>Previous C-section (%)</td>
<td>12 (14.6%)</td>
<td>4 (8.3%)</td>
<td>Not significant, p value not reported</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>----------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Median total dose of misoprostol: micrograms</td>
<td>200 micrograms</td>
<td>100 micrograms</td>
<td>p=0.0028</td>
</tr>
<tr>
<td>Median misoprostol doses</td>
<td>2</td>
<td>3</td>
<td>p=0.0019</td>
</tr>
</tbody>
</table>

**Efficacy**

<table>
<thead>
<tr>
<th>Median induction (with misoprostol) to delivery (all gestational ages): hours (range)</th>
<th>13.3 (2.1 to 97.3)</th>
<th>12.8 (3.3 to 126.9)</th>
<th>Not significant, p value not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median induction (with misoprostol) to delivery for 21 to 25 weeks gestation: hours (range)</td>
<td>17.9 (6.4 to 90.6)</td>
<td>11.2 (3.7 to 126.9)</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Median induction (with misoprostol) to delivery for 26 to 30 weeks gestation: hours (range)</td>
<td>17.6 (2.7 to 97.3) (n=23)</td>
<td>15.7 (3.2 to 35.4) (n=9)</td>
<td>Not significant, p value not reported</td>
</tr>
<tr>
<td>Median induction (with misoprostol) to delivery for 31 to 35 weeks gestation: hours (range)</td>
<td>15.7 (6.3 to 84.3) (n=16)</td>
<td>23.1 (6.1 to 59.2) (n=12)</td>
<td>Not significant, p value not reported</td>
</tr>
<tr>
<td>Median induction (with misoprostol) to delivery for 36 to 41 weeks gestation: hours (range)</td>
<td>9.5 (2.1 to 35.9)</td>
<td>12.6 (5.8 to 31.4)</td>
<td>Not significant, p value not reported</td>
</tr>
<tr>
<td>Delivery by 48 hours after the start of misoprostol</td>
<td>92.7%</td>
<td>93.5%</td>
<td>Not significant, p value not reported</td>
</tr>
<tr>
<td>% needing oxytocin administration (median dose)</td>
<td>46% (0.56 IU)</td>
<td>58% (0.65 IU)</td>
<td>Not significant, p value not reported</td>
</tr>
<tr>
<td></td>
<td>When analysed at 5-week intervals, use and dose of oxytocin was reported to be similar; figures not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Analgesia requirements**

| Nitrous oxide | 38% (31 of 82) | 52% (25 of 48) | Not significant, p value not reported |
| Epidural anaesthesia | 66% (54 of 82) | 63% (30 of 48) | Not significant, p value not reported |
| Opioid analgesia | 88% (72 of 82) | 88% (42 of 48) | Not significant, p value not reported |

**Safety**

| Maternal death | None reported | None reported |
| Need for transfusion | 2 (2.4%) | 4 (8.3%) | Not significant, p value not reported |
| | There were 4 cases in total of excessive haemorrhage (1000 ml) in the misoprostol group and 4 cases in the mifepristone plus misoprostol group |
| Fever | 2 (2.4%) | 5 (10.4%) | p=0.052 |
| Antibiotic use | 6 (7.3%) | 10 (20.8%) | p=0.024 |
| Surgical evacuation of the uterus | 6 (7.3%) | 3 (6.3%) | Not significant, p value not reported |

Abbreviations: C-section, caesarean section; IU, international units.

Note: except where stated, the results include all cases of intrauterine fetal death (IUFD), including cases between 21 and 24 weeks gestation.
Safety

**Mifepristone plus vaginal and oral misoprostol compared with mifepristone plus vaginal misoprostol**

The UK case series by Fairley et al. (2005) found that gastrointestinal adverse events were reported in 48% of the combined vaginal and oral misoprostol group and 35% of the vaginal misoprostol only group. The statistical significance of the difference was not reported.

The number of cases of postpartum haemorrhage and manual removal of the placenta was small. No cases of excessive uterine contraction frequency, uterine rupture, dehiscence, maternal coagulopathy or maternal death were reported.

**Misoprostol alone compared with mifepristone plus misoprostol**

The case series by Vayrynen et al. (2007) reported that women in the mifepristone and misoprostol group were statistically significantly more likely to need antibiotics (p=0.024) than women in the misoprostol alone group. However, the researchers reported that the rate of infections relating to delivery was no different between the groups. More women in the mifepristone and misoprostol group had fever but this was not significant (p=0.052).

The rates of other complications of delivery, including excessive haemorrhage, need for blood transfusion and surgical evacuation of the uterus, were small and similar between the groups. One case of coagulopathy was reported in the combination treatment group. Gastrointestinal adverse events were not reported.

**Summary of product characteristics**

The summary of product characteristics for the licensed oral misoprostol preparation states that diarrhoea and rash are very common adverse events (1 or more in every 10 people) associated with misoprostol use when used for the preventing and treating duodenal and gastric ulcers. Common adverse events (between 1 in 100 and 1 in 10) include dizziness, headache, abdominal pain, constipation, dyspepsia, flatulence, nausea and vomiting. The doses of misoprostol used for the licensed indications are higher than when misoprostol is used off-label for late IUFD.

The summary of product characteristics for oral misoprostol also notes that the risk of uterine rupture increases with advancing gestational age and with prior uterine surgery, including caesarean delivery.
Cost effectiveness and cost

No cost-effectiveness studies were identified that assessed the use of misoprostol for induction of labour for late IUFD compared with other treatments or placebo. No estimate of the current use of misoprostol for this indication in UK clinical practice was identified.

A pack of 60 misoprostol 200 microgram tablets (Cytotec) costs £10.03 (Drug Tariff, February 2013). At the time of publication, costs are not available for Medabon or MisoOne.

Relevance to NICE guidance programmes

The use of misoprostol for the induction of labour for late intrauterine fetal death (IUFD) is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued a clinical guideline on induction of labour (NICE clinical guideline 70).

Other NICE guidance related to the use of misoprostol includes:

- Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage (NICE clinical guideline 154)
- Intrapartum care: care of healthy women and their babies during childbirth (NICE clinical guideline 55). This guideline is currently being updated, and is expected to be published in October 2014.

Intervention and alternatives

Misoprostol is a synthetic prostaglandin E₁ analogue that softens the cervix and can stimulate uterine contractions. Prostaglandins are a group of hormone-like substances that mediate a wide range of physiological functions such as contraction of smooth muscle.

Misoprostol 200 microgram oral tablets (Cytotec, Pharmacia Limited) are licensed in the UK for treating duodenal and gastric ulcers and preventing non-steroidal anti-inflammatory drug-induced ulcers in adults.

Medabon (Sun Pharmaceutical Industries Europe) is a combination pack containing 1 oral mifepristone 200 mg tablet and 4 vaginal misoprostol 200 microgram tablets. It received UK
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MisoOne (Exelgy) contains 400 micrograms of misoprostol for oral administration. In January 2013 it was licensed in the UK for the termination of intrauterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea.

In their guideline on the management of late intrauterine fetal death and stillbirth the Royal College of Obstetricians and Gynaecologists (RCOG) advises that doses of 25 to 100 micrograms of misoprostol should be used, depending on gestational age. Guidance produced by the RCOG has been accredited by NICE. The RCOG guideline and the full NICE guideline on induction of labour state that tablets may be cut or made into suspension to achieve lower doses. However, uniform concentration and accurate drug delivery is not guaranteed.

The use of misoprostol orally, sublingually or vaginally for the induction of labour in IUFD is off-label.

**Condition**

Intrauterine fetal death (IUFD) is defined by the full NICE guideline on the induction of labour and the RCOG guideline on late intrauterine fetal death and stillbirth as fetal death at 24 weeks gestation or later. For the purposes of this evidence summary this is referred to as late IUFD.

NICE states that late IUFD is estimated to occur in 1% of all pregnancies, with over 90% of these women spontaneously delivering within 3 weeks of the intrauterine death. Particular problems related to delayed labour may arise, such as intrauterine infection if the membranes are ruptured, and a time-related risk of disseminated intravascular coagulopathy, which has been reported in 25% of women who retain a dead fetus for more than 4 weeks.

The management of induction of labour in women with late IUFD and a favourable cervix is often uncomplicated. The risks of failed induction and uterine rupture increase when the cervix is unfavourable, particularly in women with previous caesarean delivery (see the NICE full guideline on induction of labour).

**Alternative treatment options**

The NICE clinical guideline on induction of labour states that in the event of late IUFD, a woman should be offered a choice of immediate induction of labour or expectant management if she is
physically well, her membranes are intact and there is no evidence of infection or bleeding. For women who choose to proceed with induction of labour, the guideline recommends that oral mifepristone followed by vaginal prostaglandin $E_2$ or vaginal misoprostol (prostaglandin $E_1$) should be offered. The choice and dose of vaginal prostaglandin should take into account the clinical circumstances, availability of preparations and local protocol.

NICE advises that in the event of late IUFD with evidence of ruptured membranes, infection or bleeding, immediate induction of labour is the preferred management option. Support should be offered to help women and their partners and/or family cope with the emotional and physical consequences of the death.

The RCOG guideline on the management of late IUFD and stillbirth recommends that a combination of mifepristone and a prostaglandin preparation should usually be recommended as the first-line intervention for induction of labour. The RCOG advises that misoprostol (25 to 100 micrograms, depending upon gestational age) can be used in preference to prostaglandin $E_2$ because of its equivalent safety and efficacy and lower cost, although it is not currently licensed for this indication in the UK. The RCOG does not explicitly advise that vaginal misoprostol should be used. However, it does state that women should be advised that vaginal misoprostol is as effective as oral therapy but associated with fewer adverse effects.

An update to the RCOG guideline in July 2011 noted that some hospitals in the UK were using larger doses of misoprostol than recommended in the 2010 guideline, potentially leading to adverse events. The RCOG advised maternity units to review their protocols for the induction of labour after late IUFD.

This evidence summary describes the risks and benefits of vaginal misoprostol, when used after oral mifepristone according to NICE guidance on the induction of labour in late IUFD. It focusses particularly on the dose of misoprostol.

Mifepristone (Mifegyne, Exelgyn) is licensed for induction of labour in IUFD when a prostaglandin or oxytocin cannot be used.

**Evidence review: efficacy**

No randomised controlled trials were identified that compared the risks and benefits of vaginal misoprostol, when used after oral mifepristone according to NICE guidance on the induction of labour in late intrauterine fetal death (IUFD).
Two case series were found that met the inclusion criteria for this evidence review. They compared the effects of a low-dose misoprostol treatment regimen with a higher dose regimen for induction of labour after late IUFD. In both of the studies, the groups of women being examined were studied over different time periods after a change in practice in the study hospitals.

The first case series (Fairley et al. 2005) was included in the NICE clinical guideline on induction of labour. One additional study (Vayrynen et al. 2007), not included in the NICE clinical guideline on induction of labour or the RCOG guidance on late IUFD, was identified from the search.

A Cochrane review has compared the benefits and risks of misoprostol for inducing labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly, or after IUFD. None of the randomised controlled trials that it included met the criteria for this evidence summary. However, the review includes safety data on misoprostol in a relevant population; this is briefly described in the Evidence review: safety section.

**Mifepristone plus vaginal and oral misoprostol compared with mifepristone plus vaginal misoprostol**

The UK case series by Fairley et al. (2005) compared low-dose vaginal misoprostol (50 micrograms 3-hourly) with a higher dose administered both vaginally and orally (400 micrograms 4-hourly) in 47 women with late IUFD (24 weeks gestation or later). The group that used the vaginal and oral misoprostol combination (n=29) was treated between February 1998 and December 2001, whereas the group that used vaginal misoprostol alone (n=18) was treated between March 2002 and May 2003. The change in the mifepristone and misoprostol treatment regimen occurred because of reports that were published on the risk of uterine rupture with the combination of oral and vaginal misoprostol.

All women took mifepristone 200 mg orally and were admitted 36 to 48 hours later to a consultant obstetrician led delivery suite for administration of misoprostol. The therapeutic regimens were repeated after 12 hours if the first course failed to induce labour. If 2 courses of misoprostol failed, further management was decided on a case-by-case basis. The proportion of women who had 2 courses of misoprostol that failed to induce labour was not reported.

Information was collected prospectively. Outcomes included the time from administration of the first dose of misoprostol (induction) to fetal delivery, analgesic requirements and adverse events. Three women in the combined vaginal and oral misoprostol group and 1 woman in the vaginal misoprostol only group had a previous caesarean section. All women delivered vaginally.
Women in the combined vaginal and oral administration group received a higher mean total dose of misoprostol (828 micrograms) compared with the vaginal administration only group (167 micrograms). The median induction to fetal delivery interval was 7 hours (range 1.5 to 29.5) in the combined vaginal and oral administration group and 10.2 hours (range 1.5 to 20.0) in the vaginal administration only group. The statistical significance of the difference in induction to delivery time was not reported.

Twenty women (69%) in the vaginal and oral misoprostol group received parenteral opiates (morphine infusion or intramuscular diamorphine) compared with 14 (78%) in the vaginal misoprostol only group. Four women (14%) in the combined vaginal and oral misoprostol group requested epidural analgesia compared with 1 woman (6%) in the vaginal misoprostol only group, and 5 women in the combined vaginal and oral misoprostol group received oral or no analgesia (numbers not reported) compared with 3 women (17%) who received oral analgesia in the vaginal misoprostol only group. See table 1 for more details. The statistical significance of any differences between the groups was not reported.

Although women who received a higher dose of misoprostol delivered 3 hours faster on average, this study suggests that low-dose misoprostol (mean 167 micrograms) administered vaginally is effective for the induction of labour after IUFD at 24 weeks gestation or later.

**Misoprostol alone compared with mifepristone plus misoprostol**

The Finnish case series by Vayrynen et al. (2007) compared the use of vaginal misoprostol alone (between 1997 and 2001) with oral mifepristone 200 mg followed by vaginal misoprostol (between 2001 and 2005) in 130 women with IUFD. Single 4-hourly doses of 25 to 400 micrograms (median 100 micrograms) were used in the vaginal misoprostol alone group (n=82) compared with 25 micrograms in the combination treatment group (n=48). The reason for the wide variation in dose of vaginal misoprostol used in the misoprostol only group was not reported.

The study included gestational ages of 22 weeks and later (minimum 21 weeks plus 5 days), whereas the NICE and RCOG guidelines cover gestational ages of 24 weeks and later. Gestational ages below 24 weeks are outside the inclusion criteria for this evidence summary. However, subgroup analyses were performed in 5-week gestational age intervals.

Study outcomes included induction to delivery time, need for oxytocin or analgesia, and adverse events.
The median total dose of misoprostol was significantly lower in the combination mifepristone and misoprostol treatment group compared with the misoprostol alone group (100 micrograms compared with 200 micrograms, p=0.0028). However, the median number of doses needed was higher in the combination treatment group compared with the misoprostol alone group (3 compared with 2, p=0.0019).

Overall, the study found no significant difference between the groups in the induction to delivery interval. The median induction to fetal delivery interval was 12.8 hours (range 3.2 to 126.9) in the combined mifepristone and misoprostol group and 13.3 hours (range 2.1 to 97.3) in the vaginal misoprostol alone group. There were also no statistically significant differences between the combination and vaginal only groups for the subgroups of gestational ages that are directly relevant to this evidence summary (26 to 30 weeks, 31 to 35 weeks, and 36 to 41 weeks). Although the number of women in each subgroup was small, these results support the overall findings.

For the subgroup of gestational ages from 21 to 25 weeks, which has limited applicability to this evidence summary, the induction to delivery time was statistically significantly shorter in the mifepristone and misoprostol group compared with the misoprostol alone group (11.2 hours compared with 17.9 hours, p=0.04).

There was no significant difference between the groups in the proportion of women who had given birth within 48 hours of starting misoprostol therapy, or in women who needed oxytocin administration, nitrous oxide, epidural anaesthesia or opioid analgesia. See table 2 for further details.

The results of this study suggest that, when used after mifepristone according to NICE guidance, low-dose misoprostol (median 100 micrograms) is effective for the induction of labour after IUFD at 22 weeks gestation or more.

**Evidence review: safety**

*Mifepristone plus vaginal and oral misoprostol compared with mifepristone plus vaginal misoprostol*

The UK case series by Fairley et al. (2005) found that gastrointestinal adverse events were reported in 48% of the combined vaginal and oral misoprostol group and 35% of the vaginal misoprostol only group. The statistical significance of the difference was not reported.
There were 4 cases of postpartum haemorrhage (more than 1000 ml) in the combined vaginal and oral misoprostol group, 3 of whom had a blood transfusion, compared with 2 cases in the vaginal misoprostol only group who both needed blood transfusion. Manual removal of the placenta was needed in 4 women (14%) who received vaginal and oral misoprostol and in 1 woman (6%) who received only vaginal misoprostol. The statistical significance of any differences between the groups was not reported.

No cases of excessive uterine contraction frequency, uterine rupture, dehiscence, maternal coagulopathy or maternal death were reported.

**Misoprostol alone compared with mifepristone plus misoprostol**

The case series by Vayrynen et al. (2007) reported that women in the mifepristone plus misoprostol group were statistically significantly more likely to need antibiotics (p=0.024) than women in the misoprostol alone group. However, the researchers reported that the rate of infections relating to delivery was no different between the groups. More women in the mifepristone plus misoprostol group had fever but this was not statistically significant (p=0.052).

The number of women reporting other complications of delivery was small. There were no significant differences between the mifepristone plus misoprostol and misoprostol alone groups in terms of excessive haemorrhage (more than 1000 ml; 8.3% compared with 5.6% respectively), the need for blood transfusions (8.3% compared with 2.4% respectively), and the need for surgical evacuation of the uterus (6.3% compared with 7.3% respectively). One case of coagulopathy was reported in the combination treatment group. Gastrointestinal adverse events were not reported.

**Other sources of safety information**

The summary of product characteristics for the licensed oral misoprostol preparation states that diarrhoea and rash are very common adverse events (1 or more in every 10 people) associated with misoprostol use when used for preventing and treating duodenal and gastric ulcers. Common adverse events (between 1 in 100 and 1 in 10) include dizziness, headache, abdominal pain, constipation, dyspepsia, flatulence, nausea and vomiting.

The doses of misoprostol used for the licensed indications are higher than when misoprostol is used off-label for late IUFD: 800 micrograms daily for at least 4 weeks for treating duodenal and gastric ulcers, and 200 micrograms up to 4 times daily for preventing NSAID-induced ulcers. The RCOG recommends doses of 25 to 100 micrograms, depending on gestational age, for late IUFD. Diarrhoea and abdominal pain are reported as being dose related.
The summary of product characteristics for oral misoprostol also notes that risk of uterine rupture increases with advancing gestational age and with prior uterine surgery, including caesarean delivery.

The NICE full guideline for hypertension in pregnancy states that misoprostol, used in the third stage of labour, increases blood pressure more frequently than oxytocin.

A Cochrane review (38 randomised controlled trials, n=3679) compared the benefits and risks of misoprostol for inducing labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after IUFD. It found that vaginal misoprostol was associated with a reduction in the occurrence of maternal gastrointestinal side effects such as nausea, vomiting and diarrhoea, compared with other prostaglandin preparations. However, there are insufficient data to assess the occurrence of rare but potentially life-threatening complications for the woman, including uterine rupture, and further research is needed to determine the optimal dose and frequency of administration and to assess rare adverse events.

Evidence review: economic issues

Cost effectiveness

No cost-effectiveness studies were identified that assessed the use of misoprostol for induction of labour for late intrauterine fetal death (IUFD) compared with other treatments or placebo.

Cost

A pack of 60 misoprostol 200 microgram tablets (Cytotec) costs £10.03 (Drug Tariff, February 2013). At the time of publication, costs are not available for Medabon or MisoOne.

The RCOG guideline on the management of late IUFD and stillbirth recommends that the dose of misoprostol be adjusted according to gestational age: 100 micrograms 6-hourly before 26 weeks gestation, and 25 to 50 micrograms 4-hourly at 27 weeks gestation or more. This is based on a review by Gómez Ponce de León et al. (2007).

Fairley et al. (2005) used a vaginal misoprostol dosage of 50 micrograms 3-hourly and the mean dose was 167 mg. Vayrynen et al. (2007) used a misoprostol dosage of 25 micrograms 4-hourly and the median dose was 100 micrograms. Assuming that 3 or 4 doses were administered as reported in these treatment regimens, the cost per woman for the drug alone would be 50 to 67 pence (excluding VAT and allowing for wastage when splitting tablets).
Current drug usage

NHS prescription cost analysis for England 2011 reported that 11,900 prescriptions for misoprostol 200 microgram tablets were dispensed in primary care in England in 2011 at a net cost of £140,400. It is not known which indication these medications were prescribed for, but it is likely that most, if not all, of these prescriptions are for prevention of upper gastrointestinal ulcers. No estimate of the current use of misoprostol for this indication in UK clinical practice was identified.

Evidence strengths and limitations

No randomised controlled trials were identified that met the inclusion criteria for this evidence summary; the evidence is based on 2 small case series (Fairley et al. 2005 and Vayrynen et al. 2007). Both studies have limitations that affect the validity and generalisability of their findings. For example, neither of the studies was randomised; both used retrospective control groups from an earlier time period; and both included small numbers of women (n=47 and n=130, respectively). Neither study reported how the small doses of misoprostol were prepared, how acceptable vaginal use was to the women, or how satisfied they were with treatment. The statistical significance of any differences between the treatment groups was not reported in Fairley et al. (2005), which limits the conclusions that can be made.

Observational studies like these are prone to confounding. Unlike in the setting of a randomised controlled trial, in clinical practice treatment plans are chosen, changed, or actively not chosen in the light of the individual woman’s risk factors, preferences and tolerability or response to other drugs. Therefore, observed differences in outcomes may be due to differences among the women, not only the different treatments. The use of a retrospective control group is another potential source of bias. It relies on the accuracy of historical records. Also, it is possible that, in addition to the change in misoprostol treatment regimen to induce labour in IUFD, other changes in practice may have occurred between the time periods studied, which may have affected treatment outcomes.

Fairley et al. (2005) compared low-dose vaginal misoprostol with a higher dose administered both vaginally and orally in women with IUFD. Between March 2002 and May 2003, when the lower dose was studied, some women with IUFD received other treatment options, based on the preference of the senior obstetrician. Nine women received prostaglandin and oxytocin therapy, 2 received mifepristone alone, and 2 had a caesarean section. The remaining 12 women delivered spontaneously. It is unclear how the use of mifepristone and misoprostol (at high and low doses) compared with the other options because the number of women receiving those options was too small to make meaningful comparisons.
Vayrynen et al. (2007) compared the use of vaginal misoprostol alone with oral mifepristone 200 mg followed by vaginal misoprostol in women with IUFD. Although the groups were similar in terms of age, duration of pregnancy and status of the cervix, there was a higher rate of nulliparity in the combination mifepristone plus misoprostol group which the researchers say may have prolonged the induction to delivery time in this group.

These 2 case series suggest that low dose vaginal misoprostol following mifepristone is effective at inducing labour in late IUFD. Further research is needed to evaluate the safety and efficacy of different dosages of vaginal misoprostol used for this indication.

Summary for patients

A summary written for patients is available on the NICE website.

References

Dodd JM and Crowther CA (2010) Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Cochrane Database of Systematic Reviews issue 4: CD004901

Exelgyn (2012) Mifegyne summary of product characteristics [online; accessed 18 March 2013]


National Institute for Health and Clinical Excellence (2008) Induction of labour. NICE clinical guideline 70


NHS Electronic Drug Tariff for England and Wales [online; accessed 18 March 2013]


Pharmacia Limited (2013) Cytotec 200mcg tablets summary of product characteristics [online; accessed 18 March 2013]

Royal College of Obstetricians and Gynaecologists (2011) Late intrauterine fetal death and stillbirth (Green-top 55) [online; accessed 18 March 2013]


Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The interim process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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 Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- NHS Evidence
- NICE
- Euroscan
- Broad internet search: Google e.g.: allintitle: mifepristone misoprostol (stillbirth OR (death - abortion –termination) OR "missed abortion" OR intrauterine death) OR intrauterine death
- Scirus
Induction of labour in late intrauterine fetal death: vaginal misoprostol (after oral mifepristone) (ESUOM11)

MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1. Stillbirth/ (1657)
2. intrauterine death.ti,ab. (1094)
3. fetal death.ti,ab. (4896)
4. stillbirth.ti,ab. (4295)
5. Abortion, Missed/ (912)
6. missed abortion.ti,ab. (576)
7. Fetal Death/ (22307)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (29569)
9. misoprostol/ (3087)
10. misoprostol.ti,ab. (3428)
11. 9 or 10 (3865)
12. 8 and 11 (171)
13. limit 12 to english language (157)

Embase (via Ovid)

Database: Embase <1988 to 2013 February 05>

Search Strategy:

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<tr>
<td>2.</td>
<td>intrauterine death.ti,ab. (1042)</td>
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<tr>
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<td>fetal death.ti,ab. (4527)</td>
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<td>5.</td>
<td>Abortion, Missed/ (621)</td>
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<tr>
<td>6.</td>
<td>missed abortion.ti,ab. (506)</td>
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<td>7.</td>
<td>fetus death/ (11149)</td>
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<td>1 or 2 or 3 or 4 or 5 or 6 or 7 (21041)</td>
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<td>14.</td>
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</table>

**Cochrane Central Register of Controlled Trials (CENTRAL)**

#1 MeSH descriptor: [Misoprostol] explode all trees

#2 misoprostol:ti,ab

#3 #1 or #2

#4 MeSH descriptor: [Mifepristone] explode all trees

#5 mifepristone:ti,ab

#6 #4 or #5

#7 MeSH descriptor: [Fetal Death] explode all trees
Induction of labour in late intrauterine fetal death: vaginal misoprostol (after oral mifepristone) (ESUOM11)

#8 MeSH descriptor: [Stillbirth] explode all trees

#9 (fetal death):ti,ab

#10 (intrauterine death):ti,ab

#11 (foetal death):ti,ab

#12 MeSH descriptor: [Abortion, Missed] explode all trees

#13 #7 or #8 or #9 or #10 or #11 or #12

#14 #3 and #6 and #13

CRD HTA, DARE and EED database

1 MeSH DESCRIPTOR Misoprostol EXPLODE ALL TREES 69

2 (misoprostol):TI 58

3 #1 OR #2 79

4 MeSH DESCRIPTOR mifepristone EXPLODE ALL TREES 13

5 (mifepristone):TI 9

6 #4 OR #5 15

7 #3 AND #6 8

Grey literature and ongoing trials

- FDA
- EMA
- MHRA
- Scottish Medicines Consortium
Evidence selection

Studies were included based on predetermined criteria for relevance to the question set at scoping. The purpose of the evidence summary was to describe the risks and benefits of vaginal misoprostol, when used after oral mifepristone according to NICE guidance on the induction of labour in late intrauterine fetal death (IUFD). The intervention of interest was the use of vaginally delivered misoprostol after mifepristone therapy for induction of labour among women with late IUFD (24 weeks gestation or later). Studies had to contain an intervention arm in which women received vaginal misoprostol (only route of administration) following oral mifepristone to be included. Studies containing this intervention arm were included regardless of comparator. The highest quality research was selected as the basis for answering the questions set on efficacy, safety and cost. The search was initially limited to randomised controlled trials (RCTs), systematic reviews and cost studies; however, this search strategy was broadened (by removing the study types filter) to include additional study types after identification of a lack of relevant RCTs or systematic reviews. The search strategies reported above are for the broader searches.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.