NICE advice

Induction of labour: misoprostol vaginal delivery system

Evidence summary
Published: 25 March 2014
nice.org.uk/guidance/esnm38

Key points from the evidence

The content of this evidence summary was up-to-date in March 2014. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

In a randomised controlled trial of 1358 women, the misoprostol vaginal delivery system (controlled-release vaginal insert) statistically significantly reduced the time to vaginal delivery and reduced the need for oxytocin compared with the dinoprostone controlled-release vaginal insert. The rate of caesarean delivery was similar in both treatment groups, but the pre-specified criterion for non-inferiority to dinoprostone was not met. Overall, there were no significant differences between the treatment groups in the proportions of women or neonates who experienced adverse events, although there were some statistically significant differences in individual adverse events. For example, uterine hyperstimulation was significantly more common in women receiving the misoprostol vaginal insert.

Effectiveness	Safety
• In the study, compared with the dinoprostone vaginal insert, the misoprostol vaginal insert statistically significantly reduced: – the median time to vaginal delivery by 11.3 hours (p<0.001) – the median time to any delivery (vaginal or caesarean) by 9.0 hours (p<0.001) – the median time to active labour by 6.5 hours (p<0.001), and – the need for oxytocin by 26% (p<0.001).	• In the study, the rate of caesarean delivery was similar in both treatment groups (26–27%; p=0.65) but the pre-specified criterion for non-inferiority to dinoprostone was not met. • Uterine tachysystole with fetal heart rate changes or tachysystole requiring intervention was 3 times higher with misoprostol compared with dinoprostone (13.3% compared with 4.0%, p<0.001). • The summary of product characteristics states that the most common adverse events are abnormal uterine contractions, fetal heart rate disorder, abnormal labour affecting the fetus and meconium in the amniotic fluid.
Patient factors	**Resource implications**
• Prolonged labour is associated with higher infection rates, greater use of antibiotics and oxytocin, and increased maternal distress. • The time to delivery is important to women undergoing induction of labour, as are other outcomes such as the time to active labour.	• The cost of the misoprostol controlled-release vaginal insert is expected to be about £93. The costs of the dinoprostone vaginal gel, tablet and controlled-release insert range from £13.28 to £30.00. • Prolonged labour is associated with more demands on hospital resources. • Health economic analyses of the misoprostol vaginal insert are expected to be published later in 2014.

Key points

In November 2013, a UK marketing authorisation was granted for the misoprostol controlled-release vaginal delivery system (Mysodelle) for the induction of labour in women with an unfavourable cervix, from 36 weeks' gestation, in whom induction is clinically indicated. The manufacturer has advised that the UK launch is expected in quarter 4, 2014 (Ferring Pharmaceuticals: personal communication, January 2014).

Currently, only short-acting oral preparations of misoprostol are available and none is licensed for the induction of labour in the UK. In practice, oral misoprostol tablets are sometimes administered vaginally to induce labour. The tablets must be cut or made into suspension to achieve lower doses. Use of the oral preparations in this way is off-label.

EXPEDITE was a phase III, double-blind, randomised multicentre study that compared the efficacy and safety of a 200 microgram misoprostol controlled-release vaginal insert and a 10 mg dinoprostone controlled-release vaginal insert in 1358 women undergoing induction of labour. The study found that the median time to vaginal delivery (the primary efficacy outcome) was statistically significantly reduced by 11.3 hours in women who received misoprostol compared with dinoprostone. The median time from study drug administration to vaginal delivery was 21.5 hours (95% confidence interval [CI] 20.0 to 23.4 hours) for the misoprostol vaginal insert and 32.8 hours (95% CI 30.2 to 34.9 hours) for the dinoprostone vaginal insert (p<0.001).

Statistically significant improvements were also seen in the 3 key secondary efficacy end points. The median time to any delivery (vaginal or caesarean) was reduced by 9.0 hours (p<0.001); the median time to active labour was reduced by 6.5 hours (p<0.001); and the proportion of women requiring pre-delivery oxytocin was reduced by 26% (p<0.001) in women receiving the misoprostol vaginal insert compared with the dinoprostone vaginal insert.

In EXPEDITE, the rate of caesarean delivery (the primary safety end point) was similar in the misoprostol and dinoprostone groups (26.0% compared with 27.1%; difference −1.10%, 95% CI −5.79% to 3.59%; p=0.65). However, non-inferiority of the misoprostol vaginal insert to the dinoprostone vaginal insert could not be concluded because the upper limit of the 95% CI (3.59%) exceeded the pre-specified non-inferiority margin (2.71%).

Overall, there were no statistically significant differences between the treatment groups in the proportions of women or neonates who experienced adverse events, although there were some statistically significant differences in individual adverse events. The rate of uterine tachysystole with category II (indeterminate, requiring evaluation and surveillance) and category III (abnormal

and requiring prompt evaluation) fetal heart rate changes or tachysystole requiring intervention (uterine hyperstimulation) was 3 times higher with misoprostol vaginal inserts compared with dinoprostone vaginal inserts (13.3% compared with 4.0%; relative risk 3.34, 95% CI 2.20 to 5.07; p<0.001). However, rates of fetal heart rate category II and category III patterns were not statistically significantly different between the misoprostol and dinoprostone vaginal inserts.

Tocolysis use and meconium in the amniotic fluid were seen more often in the misoprostol group (both p<0.05). Arrested labour, chorioamnionitis, and intrapartum and postpartum intravenous or intramuscular antibiotic use were more common in the dinoprostone group (all p<0.05). There was no significant difference between the groups in the rate of admission to neonatal intensive care.

The EXPEDITE study was well designed and well reported, and allocation was concealed. However, the inclusion and exclusion criteria limit the generalisability of the results. For example, women aged under 18 years, women with multiple pregnancies or more than 3 previous vaginal deliveries, and women with fetal malpresentation were not included. In addition, the study was too small to assess the likelihood of rare, serious adverse perinatal and maternal complications. Post-marketing surveillance will be very important to detect potential adverse effects.

The misoprostol vaginal insert is expected to cost about £93. This is more than the costs for dinoprostone vaginal gel, tablet and controlled-release inserts, which range from £13.28 to £30.00. Although there is evidence that misoprostol reduces the median time to delivery compared with dinoprostone, it is not known whether this will have economic benefits for obstetric units by reducing the use of resources (for example, staffing) and the total cost of inducing labour, compared with current management. Health economic analyses of the misoprostol vaginal insert are expected to be published later in 2014.

The NICE clinical guideline on induction of labour (NICE clinical guideline 70) states that misoprostol (a prostaglandin E_1) should only be offered as a method of induction of labour to women who have had an intrauterine fetal death or in the context of a clinical trial. If induction of labour is clinically justified, NICE states that vaginal prostaglandin E_2 (dinoprostone gel, tablet or controlled-release insert) is the preferred method, unless there are specific clinical reasons for not using it (in particular the risk of uterine hyperstimulation). The results of EXPEDITE suggest that the risk of uterine hyperstimulation is higher with the misoprostol vaginal insert than with the dinoprostone vaginal insert.

Key evidence

Wing DA, Brown R, Plante LA et al. (2013) Misoprostol vaginal insert and time to vaginal delivery: a randomized controlled trial. Obstetrics & Gynecology 122: 201–9

Update

The following information has become available since this ESNM was produced.

November 2014: Availability of misoprostol vaginal delivery system

The misoprostol vaginal delivery system has been launched in the UK as Mysodelle 200 micrograms vaginal delivery system. The cost of Mysodelle (excluding VAT) is £465.00 for 5 delivery systems. Cost taken from MIMS, November 2014.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Relevance to NICE guidance programmes

The misoprostol vaginal delivery system was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has published relevant guidance on the care of women in labour:

- Induction of labour (NICE clinical guideline 70). A NICE pathway on induction of labour is also available.
- Intrapartum care: care of healthy women and their babies during childbirth (NICE clinical guideline 55). This guideline is currently being updated (publication expected October 2014).
- Caesarean section (NICE clinical guideline 132).

Introduction

Induced labour has an impact on the birth experience of women. It may be less efficient and is usually more painful than spontaneous labour, and epidural analgesia and assisted delivery are more likely to be required.

Induction of labour is a relatively common procedure. In 2012–2013, more than 1 in 5 deliveries in England were induced (Health and Social Care Information Centre 2013). The NICE clinical guideline on induction of labour notes that, in 2004–2005, when labour was induced using pharmacological methods (whether or not surgical induction was also attempted), less than two-thirds of women gave birth without further intervention, and about 15% of women had instrumental births and 22% had emergency caesarean sections. Induction of labour has a large impact on the health of women and their babies and so needs to be clearly clinically justified.

The NICE clinical guideline on induction of labour was published in 2008. It states that, if induction of labour is clinically justified, vaginal prostaglandin E_2 (dinoprostone) is the preferred method, unless there are specific clinical reasons for not using it (in particular the risk of uterine hyperstimulation). It should be administered as a gel, tablet or controlled-release vaginal insert. Costs may vary over time, and trusts and units should take this into consideration when prescribing vaginal prostaglandin E_2.

The 2008 NICE guideline states that misoprostol (a prostaglandin E_1) should be offered (off label) as a method of induction of labour only to women who have had an intrauterine fetal death (see also the evidence summary on Induction of labour in late intrauterine fetal death - vaginal misoprostol [after oral mifepristone]) or in the context of a clinical trial.

The Guideline Development Group for the NICE guideline considered the evidence for misoprostol for the induction of labour and concluded that vaginal misoprostol 25 micrograms was not superior to vaginal prostaglandin E_2 in women with an undefined, variable and unfavourable cervix. (An unfavourable cervix suggests that spontaneous onset of labour is unlikely. The cervix is long and firm in consistency and must be made softer and shorter to allow labour to begin.) Doses of misoprostol above 25 micrograms were associated with higher rates of successful induction of labour but at the expense of higher rates of uterine hyperstimulation. In women with a favourable cervix, there was not enough data comparing the efficacy and safety of vaginal misoprostol with other regimens to reach any conclusions.

In November 2013, a UK marketing authorisation was granted for the misoprostol controlled-release vaginal delivery system (Mysodelle) for the induction of labour in women with an unfavourable cervix, from 36 weeks' gestation, in whom induction is clinically indicated. The manufacturer has advised that the UK launch is expected in quarter 4, 2014 (Ferring Pharmaceuticals: personal communication, January 2014).

Currently, only short-acting oral preparations of misoprostol are available and none of these is licensed for the induction of labour in the UK. In practice, oral misoprostol tablets are sometimes

administered vaginally to induce labour. Tablets must be cut or made into suspension to achieve lower doses but uniform concentration and accurate drug delivery is not guaranteed. Use of the oral tablets in this way is off-label. In line with 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.

Product overview

Drug action

Misoprostol is a synthetic analogue of prostaglandin E_1, a naturally occurring oxytocic compound that softens the cervix and can stimulate uterine contractions.

Licensed therapeutic indication

The misoprostol vaginal delivery system (Mysodelle, Ferring Pharmaceuticals) is licensed for the induction of labour from 36 weeks' gestation in women with an unfavourable cervix in whom induction is clinically indicated. Contraindications include:

- active labour
- suspicion or evidence of fetal compromise before induction
- fetal malpresentation
- prior administration of oxytocic drugs or other labour induction agents
- suspicion or evidence of uterine scarring from previous uterine or cervical surgery, for example, caesarean delivery.

See the summary of product characteristics for other contraindications, warnings and precautions for use.

The misoprostol vaginal delivery system is not currently marketed in the UK. The manufacturer has advised that the UK launch is expected in quarter 4, 2014 (Ferring Pharmaceuticals: personal communication, January 2014).

Course and cost

Mysodelle is a controlled-release vaginal delivery system that releases 200 micrograms of misoprostol at a rate of approximately 7 micrograms/hour over 24 hours. The maximum recommended dose is 1 vaginal delivery system (200 micrograms).

According to the summary of product characteristics, the misoprostol vaginal delivery system should be administered only by trained obstetric personnel in a hospital setting where facilities for continuous fetal and uterine monitoring are available. The condition of the cervix should be assessed carefully before it is used. After insertion, uterine activity and fetal condition must be carefully monitored. The misoprostol vaginal delivery system should be removed at the onset of active labour; if uterine contractions are prolonged or excessive; if there is evidence of fetal compromise; or if 24 hours have elapsed since insertion. If the misoprostol vaginal delivery system falls out it should not be replaced.

The cost of the misoprostol vaginal delivery system has not yet been decided but is estimated to be £93.00 (Ferring Pharmaceuticals: personal communication, January 2014).

Evidence review

The EXPEDITE study (Wing D et al. 2013)

- Design: phase III, double-blind, randomised multicentre (35 centres in the USA) study.
- Population: the study included 1358 women (41% white) aged at least 18 years (median age 25 years; range 18 to 46 years), of parity 3 or less with singleton pregnancies (66% nulliparous), and of at least 36 weeks' gestation (mean 39.5 weeks). Women were included if they had an unfavourable cervix (baseline modified Bishop score of 4 or less; median 2) and a body mass index of 50 kg/m^2 or less (mean 34 kg/m^2). Exclusion criteria included active labour, uterine or cervical scarring or other uterine abnormality, fetal malpresentation and evidence of fetal compromise at baseline.
- Intervention and comparison: women were randomised to receive either a 200 microgram misoprostol controlled-release vaginal insert or a 10 mg dinoprostone controlled-release vaginal insert (Propess) that were identical in appearance. Allocation was concealed. Demographic and baseline characteristics were not significantly different between the groups.
- Follow-up: women remained in bed for at least 30 minutes after insertion of the drug. They were continuously monitored for uterine and fetal heart rate activity. Vaginal examinations

were performed at 6, 12, 18 and 24 hours if delivery had not occurred, even if the insert had been removed, the woman was in active labour or a caesarean delivery was planned. The vaginal insert was removed at the onset of active labour; at the completion of the 24-hour dosing period; at the occurrence of any intrapartum adverse event; or at the woman's request. Oxytocin administration was permitted 30 minutes after removal of the insert if the woman was not in active labour and her fetus's status was reassuring. Women and neonates were observed for adverse events until hospital discharge; information was also collected on neonatal admissions and emergency room visits within 1 month of birth.

- Outcomes: the primary efficacy measure was the time from study drug administration to vaginal delivery of the neonate. The primary safety measure was the rate of caesarean delivery. Key secondary efficacy end points were time to any delivery (vaginal or caesarean), time to onset of active labour, and the proportion of women requiring pre-delivery oxytocin. The proportion of women with vaginal delivery and any delivery within 12–24 hours was also assessed but is not discussed in this evidence summary. In addition to the rate of caesarean delivery, safety was assessed by comparing the incidences of intrapartum, maternal postpartum and neonatal adverse events. Efficacy analyses were performed using the intention-to-treat population, which included all randomised women who received the study drug. The safety population includes all women who received the study drug and their neonates.

Table 1 Summary of EXPEDITE (Wing D et al. 2013)

	Misoprostol 200 micrograms	Dinoprostone 10 mg	Analysis
Randomised	n=678	n=680	
Efficacy[a]	n=678	n=680	
Primary efficacy outcome: median time to vaginal delivery (hours)	21.5 (95% CI 20.0 to 23.4)	32.8 (95% CI 30.2 to 34.9)	Difference −11.3 hours p<0.001
Selected secondary outcomes:			
Median time to vaginal or caesarean delivery (hours)	18.3 (95% CI 17.2 to 19.5)	27.3 (95% CI 26.2 to 28.9)	Difference −9.0 hours p<0.001

Median time to active labour (hours)	12.1 (95% CI 12.0 to 12.9)	18.6 (95% CI 18.1 to 22.5)	Difference −6.5 hours p<0.001
Women requiring pre-delivery oxytocin[b]	48.1% (324/674)	74.1% (497/671)	Difference −26% p<0.001
Safety[c]	n=678	n=680	
Primary safety outcome: rate of caesarean delivery	26.0% (176/678)	27.1% (184/680)	Difference −1.10% (−5.79% to 3.59%) p=0.65[d]
Adverse events that resulted in a caesarean delivery	25.1% (170/678)	24.7% (168/680)	p value not reported
Adverse events in the intrapartum period[e]	55.5%	54.6%	p=0.74
Adverse events in the postpartum period[e]	21.4%	21.2%	p=0.95
Adverse events in the neonatal period[e]	53.4%	58.1%	p=0.09
Uterine tachysystole with category II or III fetal heart rate changes or tachysystole requiring intervention[f]	13.3% (90/678)	4.0% (27/680)	RR 3.34 (95% CI 2.20 to 5.07) p<0.001
Tocolysis use[g]	12.2% (83/678)	4.1% (28/680)	RR 2.97 (95% CI 1.96 to 4.50) p<0.05
Meconium in amniotic fluid[h]	17.7% (120/678)	13.5% (92/680)	RR 1.31 (95% CI 1.02 to 1.68) p<0.05

Arrested labour (dilation or descent)	14.2% (96/678)	18.8% (128/680)	RR 0.75 (95% CI 0.59 to 0.96) p<0.05
Chorioamnionitis[i]	5.6% (38/678)	8.7% (59/680)	RR 0.65 (95% CI 0.44 to 0.96) p<0.05
Intrapartum IV or IM antibiotic use	5.6% (38/678)	8.7% (59/680)	RR 0.65 (95% CI 0.44 to 0.96) p<0.05
Postpartum IV or IM antibiotic use	4.6% (31/678)	8.4% (57/680)	RR 0.55 (95% CI 0.36 to 0.83) p<0.05

Abbreviations: CI, confidence interval; IM, intramuscular; IV, intravenous; p, p value; RR, relative risk.

[a] Efficacy analyses were performed using the intention-to-treat population, which included all randomised women who received the study drug.

[b] 14 women did not deliver after their first induction attempt.

[c] The safety population includes all women who received the study drug and their neonates.

[d] Non-inferiority of misoprostol could not be concluded for this co-primary end point based on the pre-specified non-inferiority margin.

[e] Numbers of events not reported.

[f] Tachysystole (uterine hyperstimulation) was defined as 5 or more contractions in 10 minutes over 3 consecutive 10-minute periods.

[g] Tocolysis may be used to suppress contractions if uterine hyperstimulation occurs during induction of labour.

[h] Meconium in the amniotic fluid can indicate fetal distress, and can cause problems to the neonate if it is inhaled during labour.

[i] Chorioamnionitis is inflammation of the fetal membranes caused by bacterial infection. It may also affect the placenta.

Clinical effectiveness

In EXPEDITE, the median time from study drug administration to vaginal delivery (the primary efficacy outcome) was statistically significantly reduced by 11.3 hours in women undergoing induction of labour who received a 200 microgram misoprostol controlled-release vaginal insert (n=678) compared with a 10 mg dinoprostone controlled-release vaginal insert (n=680). The median time from study drug administration to vaginal delivery for women of any parity was 21.5 hours (95% confidence interval [CI] 20.0 to 23.4 hours) for the misoprostol vaginal insert and 32.8 hours (95% CI 30.2 to 34.9 hours) for the dinoprostone vaginal insert (p<0.001).

The median time to vaginal delivery was also statistically significantly shorter in women receiving the misoprostol vaginal insert compared with the dinoprostone vaginal insert in both the nulliparous (n=892; 29.2 hours compared with 43.1 hours; difference 13.9 hours, p<0.001) and parous (n=466; 13.4 hours compared with 20.1 hours; difference 6.7 hours, p<0.001) subgroups.

Statistically significant improvements were also seen in the 3 key secondary efficacy end points. The median time to any delivery (vaginal or caesarean) was reduced by 9.0 hours (p<0.001); the median time to active labour was reduced by 6.5 hours (p<0.001); and in those women who delivered after the first induction attempt the proportion requiring pre-delivery oxytocin was reduced by 26% (p<0.001) with the misoprostol vaginal insert compared with the dinoprostone vaginal insert. See table 1 for more information.

A Cochrane systematic review found that vaginal misoprostol in dosages ranging from 25 micrograms 2 to 3 hourly, to 50 micrograms 4 hourly (most studies), to 100 micrograms 6 to 12 hourly, appeared to be more effective than oxytocin or dinoprostone for induction of labour. Lower dosage regimens of misoprostol were not less effective than higher doses in terms of failure to achieve vaginal birth within 24 hours.

This review was assessed as being up to date in May 2009. An updated search was performed in February 2012 and a large number of studies have been added to the awaiting classification section of the review. These may alter the conclusions of the review once assessed.

Safety

In EXPEDITE, the rate of caesarean delivery (the primary safety end point) was similar in the misoprostol and dinoprostone groups (26.0% compared with 27.1%; difference −1.10%, 95% CI −5.79% to 3.59%); p=0.65). However, non-inferiority of the misoprostol vaginal insert to the

dinoprostone vaginal insert could not be concluded because the upper limit of the 95% CI (3.59%) exceeded the pre-specified non-inferiority margin (2.71%).

Adverse events were the most common reason for caesarean delivery in women treated with misoprostol and dinoprostone vaginal inserts (25.1% compared with 24.7% respectively; p value not reported). Other reasons were elective caesarean (0.1% compared with 0.9% respectively) and lack of efficacy (0.7% compared with 1.5% respectively).

Although the majority of adverse events leading to caesarean delivery were reported at similar rates in both groups and considered unrelated to the study drug, there were some differences between the groups. In the misoprostol group, category II fetal heart rate patterns (indeterminate, requiring evaluation and surveillance; 9.1% compared with 6.2% in the dinoprostone group) and uterine tachysystole with late decelerations, bradycardia or prolonged decelerations (1.9% compared with 0% in the dinoprostone group) were more common. Arrest of dilation or failure to dilate was more common in the dinoprostone group (12.5% compared with 8.6% in the misoprostol group). The statistical significance of these differences was not reported.

No fetal, maternal or neonatal deaths were reported and there were no significant differences between misoprostol and dinoprostone in the proportions of women or neonates who experienced any adverse events (not just those requiring caesarean delivery; see table 1 for more details). Rates of admission to neonatal intensive care, and the proportions of neonates with a low Apgar score at 1 minute or 5 minutes were similar between the groups.

Uterine tachysystole with category II or III fetal heart rate changes or tachysystole requiring intervention (uterine hyperstimulation) occurred in statistically significantly more women receiving misoprostol compared with dinoprostone (13.3% compared with 4.0%; relative risk 3.34, 95% CI 2.20 to 5.07; $p<0.001$). However, overall rates of fetal heart rate category II and category III (abnormal and requiring prompt evaluation) adverse events were not statistically significantly different between the misoprostol and dinoprostone vaginal inserts.

Tocolysis use and meconium in the amniotic fluid were seen statistically significantly more often in the misoprostol group (both $p<0.05$). Arrested labour, chorioamnionitis, and intrapartum and postpartum intravenous or intramuscular antibiotic use were more common in the dinoprostone group (all $p<0.05$). More information is available in table 1.

The Cochrane systematic review found that vaginal misoprostol in dosages ranging from 25 micrograms 2 to 3 hourly, to 50 micrograms 4 hourly (most studies), to 100 micrograms 6 to 12 hourly, statistically increased rates of uterine hyperstimulation. The trials included in the

systematic review were not sufficiently large to assess the likelihood of uncommon, serious adverse perinatal and maternal complications. Adverse events were reduced with lower dosage regimens of misoprostol, with lower rates of uterine hyperstimulation and a trend to fewer admissions to neonatal intensive care. Concern was raised over several reports of uterine rupture after misoprostol use in women with and without previous caesarean section, and the increase in meconium in the amniotic fluid. Note that the unblinded nature of the studies included in the Cochrane review raises the likelihood of bias.

The summary of product characteristics for Mysodelle states that, according to 5 clinical studies (n=874), the most common adverse events, with an incidence of between 1 in 10 and 1 in 100, are abnormal uterine contractions, fetal heart rate disorder, abnormal labour affecting the fetus and meconium in the amniotic fluid.

Evidence strengths and limitations

The EXPEDITE study was well designed and well reported. It was a relatively large randomised, blinded, controlled study, allocation was concealed and analyses were by intention-to-treat. However, Ferring Pharmaceuticals provided funding for the study and all but 1 of the 6 authors were either employees of the company or had received research support.

The inclusion and exclusion criteria may limit the generalisability of the results of the study; for example, the requirement for women to have an unfavourable cervix (modified Bishop score 4 or less; median 2) and the exclusion of any fetus–woman pair with evidence of fetal compromise at baseline. The summary of product characteristics for Mysodelle points out that the safety and efficacy of the misoprostol vaginal insert has not been established in pregnant women aged under 18 years. Similarly, it has not been studied in women whose membranes have been ruptured for more than 48 hours before insertion, in multiple pregnancies, in women with more than 3 previous vaginal deliveries after 24 weeks' gestation, or in fetal malpresentation.

The study was too small to assess the likelihood of rare, serious adverse perinatal and maternal complications. Randomised trials large enough to assess rare events such as uterine rupture are not feasible. Post-marketing surveillance will be very important to detect potential adverse effects.

Context

Treatment alternatives

If induction of labour is clinically justified, the NICE clinical guideline on induction of labour states that vaginal prostaglandin E_2 (dinoprostone) is the preferred method, unless there are specific clinical reasons for not using it (in particular the risk of uterine hyperstimulation). It should be administered as a gel, tablet or controlled-release insert. Costs may vary over time, and trusts and units should take this into consideration when prescribing vaginal prostaglandin E_2. The recommended regimens are:

- vaginal prostaglandin E_2 tablets or gel: 1 dose, followed by a second dose after 6 hours if labour is not established (up to a maximum of 2 doses)
- prostaglandin E_2 controlled-release vaginal insert: 1 dose over 24 hours.

NICE advises that oral, intravenous, extra-amniotic and intracervical prostaglandin E_2, and intravenous oxytocin alone should not be used for the induction of labour. Misoprostol or mifepristone should be offered as a method of induction of labour only to women who have had an intrauterine fetal death or, for misoprostol, in the context of a clinical trial.

Costs of treatment alternatives

	Usual dose[a]	**Estimated cost excluding VAT**[b]
Misoprostol 200 micrograms controlled-release vaginal insert	1 dose over 24 hours	£93[c]
Dinoprostone 10 mg controlled-release vaginal insert	1 dose over 24 hours	£30.00
Dinoprostone 3 mg vaginal tablet	1 dose, followed by a second dose after 6 hours if labour is not established (up to a maximum of 2 doses)	£13.28 to £26.56

Dinoprostone 1 mg or 2 mg vaginal gel	1 dose, followed by a second dose after 6 hours if labour is not established (up to a maximum of 2 doses)	£13.28 to £26.56

[a] Doses taken from the summaries of product characteristics and recommendations in the NICE clinical guideline on induction of labour. The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

[b] Costs taken from MIMS, January 2014.

[c] Ferring Pharmaceuticals: personal communication, January 2014.

Ferring Pharmaceuticals, the UK marketing authorisation holder, has advised that the misoprostol vaginal insert is likely to be more expensive than dinoprostone, but suggests it might offer economic benefits for obstetric units in terms of a reduction in the use of resources (for example, staffing) and the total cost of inducing labour, compared with current management. This is because the median time to vaginal delivery is reduced by 11.3 hours (13.9 hours in nulliparous women and 6.7 hours in parous women) with misoprostol compared with dinoprostone, and the need for oxytocin and intrapartum and postpartum intravenous or intramuscular antibiotics is lower (Ferring Pharmaceuticals: personal communication, January 2014). However, uterine tachysystole requiring intervention and use of tocolysis were about 3 times higher in the misoprostol group compared with the dinoprostone group and further evidence on cost effectiveness is needed to support this claim. Health economic analyses of the misoprostol vaginal insert are expected to be published later in 2014.

Estimated impact for the NHS

Likely place in therapy

Prolonged labour is associated with higher infection rates, greater use of antibiotics, increased maternal distress, more use of oxytocin, and more demands on staff and hospital resources. The time to delivery is important to women undergoing induction of labour, as are other outcomes such as the time to active labour, the rate of caesarean delivery and other adverse events (Shetty et al. 2005).

The misoprostol controlled-release vaginal insert offers advantages over the dinoprostone controlled-release vaginal insert in terms of substantially reduced time to vaginal or any delivery, and reduced need for oxytocin. However, the rate of uterine hyperstimulation was about 3 times higher with misoprostol vaginal inserts compared with dinoprostone vaginal inserts. The study authors note that use of the misoprostol vaginal insert therefore requires careful monitoring with

timely recognition of tachysystole affecting the fetus and implementation of appropriate interventions, which may include caesarean delivery.

The misoprostol vaginal insert is expected to cost about £93. This is more than the dinoprostone vaginal gel, tablet and controlled-release inserts, which range in cost from £13.28 to £30.00. Although there is evidence that misoprostol reduces the median time to delivery compared with dinoprostone, it is not known whether this will confer economic benefits for obstetric units in terms of a reduction in the use of resources (for example, staffing) and the total cost of inducing labour, compared with current management. Health economic analyses of the misoprostol vaginal insert are expected to be published later in 2014.

Note that licensed indications for products vary. For example, the dinoprostone controlled-release vaginal insert is licensed for the induction of labour from 38 weeks' gestation, whereas the misoprostol vaginal insert is licensed from 36 weeks' gestation. Dinoprostone may be used in women with a favourable or unfavourable cervix; misoprostol is indicated only in women with an unfavourable cervix.

The 2008 NICE clinical guideline on induction of labour states that misoprostol (a prostaglandin E_1) should only be offered as a method of induction of labour to women who have had an intrauterine fetal death or in the context of a clinical trial. If induction of labour is clinically justified, NICE states that vaginal prostaglandin E_2 (dinoprostone gel, tablet or controlled-release insert) is the preferred method, unless there are specific clinical reasons for not using it (in particular the risk of uterine hyperstimulation). The results of EXPEDITE suggest that the risk of uterine hyperstimulation is higher with the misoprostol vaginal insert than with the dinoprostone vaginal insert.

Estimated usage

It is difficult to provide estimated usage based on the available data.

According to NHS maternity statistics, 671,255 babies were delivered in NHS hospitals in England, 2012–2013. When the method of onset of labour was known, 64% of deliveries were spontaneous onset; 12.8% were medically induced; 12.7% were caesarean onset; 5.5% were medically and surgically induced; and 5.0% were surgically induced (Health and Social Care Information Centre 2013).

Currently, vaginal prostaglandin E_2 is the preferred method of induction of labour unless there are specific clinical reasons for not using it (Induction of labour, NICE clinical guideline 70). The manufacturer of the misoprostol vaginal insert, Ferring Pharmaceuticals, estimates that two-thirds

of the 23.3% of inductions (medical and/or surgical) are eligible for medical induction with vaginal prostaglandin E_2, suggesting that the estimated patient population for medical induction of labour in England is about 100,000 women per year.

It is unclear how many of these women might receive the misoprostol vaginal insert rather than vaginal prostaglandin E_2, particularly because the contraindications for the 2 drugs are similar.

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Changes after publication

24 November 2014: Minor maintenance.

3 March 2015: Minor maintenance.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be

of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – integrated process statement.

ISBN: 978-1-4731-0507-2