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Authors:

Shirley M

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Dinoprostone Vaginal Insert: A Review in Cervical Ripening

Matt Shirley[1]

Abstract

Dinoprostone vaginal insert (Cervidil®; Propess®), a retrievable vaginal pessary containing 10 mg of dinoprostone [prostaglandin E_2 (PGE_2)] in a controlled-release drug delivery device, is approved in many countries worldwide for the initiation (or continuation) of cervical ripening in patients at term prior to labour induction. The device is designed to provide a constant and sustained release of dinoprostone to the cervix to promote the complex processes involved in cervical ripening. The vaginal insert is attached to a retrieval system that facilitates easy removal of the device at the onset of labour or in the event of complications. The effectiveness of dinoprostone vaginal insert has been demonstrated in a vast range of randomized clinical trials in women at term. The agent is well tolerated, with a generally favourable safety profile, both maternal and foetal/neonatal. As with all prostaglandin agents used in cervical ripening, dinoprostone vaginal insert is associated with a risk of uterine hyperstimulation. However, this is generally rapidly reversible upon removal of the insert. The demonstrated effectiveness and safety of the device, combined with the benefits of controlled drug release from a simple, single application, and efficient dose control, suggest that dinoprostone vaginal insert is a valuable option for promoting cervical ripening in patients with an unfavourable cervix at term.

Dinoprostone Vaginal Insert: clinical considerations in cervical ripening
Drug delivery device containing dinoprostone (PGE_2) 10 mg, which is released in a controlled and constant manner
Effective in promoting cervical ripening prior to labour induction in women at term
Retrieval system enables easy removal of the device at the onset of labour or in the event of complications
Generally safe and well tolerated; can cause uterine hyperstimulation, although this is generally rapidly reversed upon device removal

The manuscript was reviewed by: ***Ż. Kimber-Trojnar***, Chair and Department of Obstetrics and Perinatology, Medical University of Lublin, Lublin, Poland; ***A. Rouzi***, Department of Obstetrics and Gynecology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

✉ Matt Shirley
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Introduction

Labour induction, or the artificial initiation of labour, is a widely used practice for the delivery of babies at term, employed in up to 25% of deliveries in developed countries [1]. Although generally lower, the rates of labour induction in developing countries are still substantial and are rising. Conditions that could be indications for labour induction include post-term pregnancy, premature rupture of membranes, preeclampsia, maternal medical conditions (e.g. diabetes) or foetal compromise (e.g. intrauterine growth restriction, oligohydramnios) [2]. In addition, a recent study has shown that induction of labour at 39 weeks in low-risk nulliparous women can result in a lower frequency of caesarean delivery compared with expectant management [3].

Prior to labour and delivery, the cervix normally undergoes the process of ripening, which refers to the softening, thinning and dilating of the cervix to enable passage of the foetus [2]. Cervical ripeness is typically assessed using the modified Bishop scoring system, in which a score is generated based on the dilation, effacement, station, position and consistency of the cervix [4]. A Bishop score of ≤ 6 is generally considered to indicate an unfavourable or unripe cervix [2, 5, 6]. In the absence of a ripe or favourable cervix the likelihood of a successful vaginal delivery is decreased. Therefore, if ripening has not occurred naturally prior to

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labour induction, use of pharmacological or mechanical methods for ripening may be indicated [2, 5, 6].

Cervical ripening is governed by prostaglandins, naturally occurring hormone-like compounds that are found throughout the body [6, 7]. In parturition, prostaglandins act through a number of different mechanisms to stimulate cervical remodelling, as well as other processes such as uterine contractions. Mechanical methods used for cervical ripening (e.g. membrane sweeping or stripping, or the use of Foley or double-balloon catheters or osmotic dilators) function in part by promoting the local release of endogenous prostaglandins [1, 5, 6]. The most commonly used pharmacological method for cervical ripening involves the administration of an exogenous prostaglandin (either dinoprostone or misoprostol). Oxytocin is not considered an effective agent for cervical ripening specifically as it is not directly involved in the process of ripening; however, given its action in stimulating uterine contractions, oxytocin is commonly used to complement cervical ripening methods (or alone, if the cervix is favourable) for the induction or augmentation of labour [1, 2, 5, 8].

The prostaglandin agents used for cervical ripening are dinoprostone, a synthetic preparation that is chemically identical to naturally occurring prostaglandin E_2 (PGE_2), and misoprostol, a synthetic prostaglandin E_1 analogue [7]. Dinoprostone is approved in many countries as endocervical gel, vaginal tablet and vaginal insert formulations for cervical ripening prior to labour induction [1, 2, 5, 8]. A misoprostol vaginal insert has been approved in several European countries since 2013 for induction of labour in women with an unfavourable cervix [9]. In tablet form, misoprostol is approved in the USA (and other countries) for reducing the risk of NSAID-induced gastric ulcers [10]. In 2017, the misoprostol tablet formulation was approved in several European countries for induction of labour in women with an unfavourable cervix [11], but it has been extensively used off-label for labour induction (through oral or vaginal administration) worldwide for many years [1, 2, 5].

This article focuses on dinoprostone vaginal insert (Cervidil® [12]; Propess® [13]), a retrievable vaginal pessary containing 10 mg of dinoprostone in a controlled-release drug delivery device. Dinoprostone vaginal insert is approved in several countries of the EU [13], in the USA [12] and in a number of other countries throughout the world for use in cervical ripening. This article reviews the efficacy, safety and tolerability of dinoprostone vaginal insert in this indication. The pharmacological properties of the agent are also discussed.

2 Pharmacological Properties of Dinoprostone Vaginal Insert

Dinoprostone is a synthetic preparation that is chemically and structurally identical to PGE_2, a naturally occurring compound that functions as a local hormone [12, 14]. Endogenous PGE_2 is present in low concentrations in most tissues of the body. As a local hormone, it is rapidly metabolized (estimated half-life < 5 min) to inactive compounds, primarily in the tissue where it is synthesized, with 15-hydroxyprostaglandin dehydrogenase functioning as a key enzyme in the metabolism. Any PGE_2 that is not inactivated locally is rapidly cleared from the circulation [12, 14], with extensive metabolism in the lungs followed by further metabolism of the resulting products in the liver and kidneys [15].

PGE_2 plays a key role in cervical ripening and parturition [7]. In pregnancy, PGE_2 is produced in the cervix, uterus and placenta as well as being secreted continuously by the foetal membranes [7, 12]. Furthermore, prostaglandin receptors have been localized to the cervix, myometrium, placenta and foetal membranes [7]. Local effects of PGE_2 include changes in cervical consistency, dilation and effacement [12]. PGE_2 can also initiate uterine contractions, including by stimulating endogenous prostaglandin $F_{2\alpha}$ production and sensitizing the myometrium to the effects of endogenous or exogenous oxytocin [12]. In some cases, uterine hyperstimulation can occur (see Sect. 4). In addition, PGE_2 plays a role in modulating the inflammatory processes that occur with cervical ripening [7].

Dinoprostone vaginal insert contains 10 mg of dinoprostone dispersed throughout the matrix of a thin flat polymeric hydrogel drug delivery device [12, 14]. The delivery system is designed to maintain a controlled and constant release of dinoprostone from the reservoir. In women with intact membranes the release rate is ~ 0.3 mg/h [12, 14], although in women with premature rupture of membranes the release of dinoprostone can be faster and more variable [16]. In one study of 24 women with uncomplicated singleton pregnancies at term who were administered dinoprostone vaginal insert, mean plasma levels of the stable PGE_2 metabolite 11-deoxy-13,14-dihydro-15-keto-11β, 16ε-cyclo PGE_2 (PGE_M) increased from 187 ± 42 (SE) pg/mL at baseline to 548 ± 110 pg/mL at 12 h ($p < 0.05$) [17]. It has not, however, been possible to determine the relative contributions of exogenous PGE_2 (dinoprostone) and endogenous PGE_2 to the plasma levels of PGE_M [12, 14]. Moreover, it is uncertain as to the extent that the measured levels of PGE_M represent an increase over the natural progression or increase that occurs as birth approaches, or over levels that might be observed in control subjects [12]. In the study, peak levels of PGE_M (measured as a marker

of PGE_2 quantities) were found to correlate with changes (improvements) in Bishop scores ($p < 0.01$; $R = 0.56$) [17]. There was also some evidence that higher increases in PGE_M levels may be associated with an increased risk of tachysystole. Mean progesterone levels were found to decline significantly ($p < 0.05$) from baseline at 4 and 8 h after insert placement whereas there was no marked change in mean dehydroepiandrosterone sulphate levels over 16 h; mean levels of unconjugated oestriol trended downwards over the initial 16 h without reaching statistical significance [18].

No changes were observed in blood flow velocities in uterine and foetal circulations [19] and no adverse effects on foetal blood gas parameters were observed in patients at term who were administered dinoprostone vaginal insert [20].

Although no specific interaction studies have been performed with dinoprostone vaginal insert, it should be noted that dinoprostone can potentiate the uterotonic effect of oxytocic agents [12, 14]. Therefore, dinoprostone vaginal insert should not be used concomitantly with oxytocic drugs (see Sect. 5).

3 Efficacy of Dinoprostone Vaginal Insert

The efficacy of dinoprostone vaginal insert in cervical ripening and labour induction has been extensively examined in a wide range of randomized controlled trials. Discussion in this section generally focuses on the larger trials, as well as on some meta-analyses that have been conducted. Inclusion/exclusion criteria for participants varied by trial. Generally, participants had singleton pregnancies at term (generally ≥ 37 weeks' gestation) with cephalic presentation, a reactive foetal heart rate (FHR) pattern/reassuring foetal status and an unfavourable cervix (generally a Bishop score ≤ 6 but in many cases a Bishop score ≤ 4) requiring ripening prior to induction of labour. Most (but not all) trials were restricted to women with intact membranes. Across the trials, reasons for induction included a gestation > 40 weeks, preeclampsia, oligohydramnios, ruptured membranes, hypertension, diabetes, intrauterine growth restriction, macrosomia, or elective induction. In the trials, administration of dinoprostone (10 mg) vaginal insert was performed through placement of the insert in the posterior vaginal fornix (using a small amount of water soluble gel if required). Generally, the insert could remain in place for up to 12 or 24 h (depending on the trial) but was removed at the onset of active labour or at the occurrence of intrapartum adverse events. Key efficacy endpoints that were assessed in different trials included measures of cervical ripening (see Sect. 3.1), the time from treatment initiation to (vaginal) delivery, vaginal delivery in ≤ 12 h or ≤ 24 h, route of delivery and requirement for oxytocin augmentation.

3.1 Comparisons with Placebo

The efficacy of dinoprostone in a vaginal insert formulation in cervical ripening and labour induction was first established in early placebo-controlled trials. Three randomized, double-blind, placebo-controlled trials of similar design were conducted, with 245 participants in total receiving dinoprostone vaginal insert and 244 receiving placebo [21–23]. In the primary efficacy measure in each of the trials, treatment success (defined as a Bishop score of ≥ 6 at 12 h, an increase in Bishop score of ≥ 3 at 12 h or vaginal delivery within 12 h of insert placement) was achieved by a significantly ($p < 0.01$) higher proportion of dinoprostone vaginal insert recipients (65–73% across the three trials) compared with placebo recipients (21–44%). Other efficacy measures also favoured dinoprostone vaginal insert over placebo.

3.2 Comparisons with Misoprostol Formulations

Numerous randomized controlled trials have compared dinoprostone vaginal insert with misoprostol in cervical ripening, with a variety of misoprostol doses, formulations and routes of administration used (Tables 1 and 2). In terms of key outcomes, most trials have concluded that dinoprostone vaginal insert has similar efficacy to the misoprostol comparator, although some trials found misoprostol to be more effective than dinoprostone vaginal insert in some efficacy outcomes, particularly when misoprostol is used at higher dosages (Tables 1 and 2).

In the two largest individual randomized controlled trials conducted to date that involved dinoprostone vaginal insert, the drug product was compared with an investigational misoprostol vaginal insert with 50 and 100 µg [MVI study ($n = 1308$)] [24] and 200 µg [EXPEDITE study ($n = 1358$)] [25] dose reservoirs. (The misoprostol 200 µg vaginal insert has subsequently been approved for use in a number of countries [11].) Both the MVI and EXPEDITE studies were double-blind, phase III trials and were conducted in the USA and Canada, and the USA, respectively. Participants in the trials were women (aged ≥ 18 years) of parity three or less with singleton pregnancies (≥ 36 weeks, 0 days' gestation) who required cervical ripening (modified Bishop score ≤ 4) before labour induction. Exclusion criteria included active labour; uterine or cervical scarring, or other uterine abnormality; severe preeclampsia with CNS involvement, or marked by haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome; receipt of any cervical ripening or labour inducing agent within 7 days of enrolment; and any condition requiring urgent delivery. In

Table 1 Key efficacy outcomes in the MVI [24] and EXPEDITE [25] trials comparing dinoprostone and misoprostol vaginal inserts[a]

Outcome	MVI trial			EXPEDITE trial	
	DVI ($n=436$)	MVI 50 µg ($n=443$)	MVI 100 µg ($n=428$)	DVI ($n=680$)	MVI 200 µg ($n=678$)
Median time to vaginal delivery [h (95% CI)]					
All participants[b]	27.5 (25.2–30.4)[†]	35.5 (33.0–37.6)	26.6 (24.5–29.0)	32.8 (30.2–34.9)	21.5 (20.0–23.4)*
Nulliparous	35.5 (31.9–42.5)	43.7 (38.0–52.4)	35.1 (30.6–43.9)	43.1 (37.9–48.8)	29.2 (25.4–32.7)*
Parous	17.6 (16.0–19.9)[‡]	25.1 (21.4–29.6)	18.0 (16.9–19.7)	20.1 (17.8–22.8)	13.4 (12.5–14.8)*
Achieving composite modified Bishop score at 12 h (%)[c]	59.6	50.3	59.3		
Need for oxytocin augmentation (%)	69.0	80.1	68.5	74.1	48.1*
Median time to onset of active labour [h (95% CI)]	15.4 (14.2–17.1)	22.3 (19.8–24.2)	15.4 (14.2–17.1)	18.6 (18.1–22.5)	12.1 (12.0–12.9)*
Median time to any delivery [h (95% CI)]				27.3 (26.2–28.9)	18.3 (17.2–19.5)*
Any delivery in ≤ 12 h (%)				9.3	23.2*
Vaginal delivery in ≤ 12 h (%)	16.5	7.5	11.9	8.4	19.8*
Any delivery in ≤ 24 h (%)				40.7	67.7*
Vaginal delivery in ≤ 24 h (%)	60.2	41.8	61.3	34.0	54.6*
Vaginal delivery (%)	72.9	71.1	71.7	71.6	73.3
Caesarean section (%)[d]	27.1	28.9	28.3	27.1	26.0

DVI dinoprostone 10 mg vaginal insert, *MVI* misoprostol vaginal insert

[†]$p=0.01$, [‡]$p<0.001$ vs. MVI 50 µg; *$p<0.001$ vs. DVI

[a]MVI was an investigational agent (although MVI 200 µg is now approved in several European countries [11])

[b]Primary efficacy endpoint for both trials

[c]Vaginal delivery in ≤ 12 h, increasing the modified Bishop score by ≥ 3 from baseline or achieving a modified Bishop score of ≥ 6

[d]Co-primary (safety) endpoint

both studies, enrolment was stratified by parity to achieve an approximate 60% to 40% ratio of nulliparous to parous women. Dinoprostone and misoprostol inserts, which were identical in appearance, were administered according to random assignment. The insert could remain in place for up to 24 h but was removed at the onset of active labour, at the occurrence of a maternal or foetal complication or intrapartum adverse event, or if it fell out of place spontaneously. The primary efficacy endpoint in each study was the time from study drug administration to vaginal delivery. In both trials, demographic and baseline obstetric characteristics of study participants were well balanced across treatment groups [24, 25].

Key efficacy outcomes of the MVI and EXPEDITE studies are shown in Table 1. In summary, dinoprostone vaginal insert had similar efficacy to the misoprostol 100 µg vaginal insert [24], whereas the misoprostol 200 µg insert significantly reduced the median time to vaginal delivery and the median time to the onset of active labour compared with the dinoprostone vaginal insert [25]. The dinoprostone insert was more effective than the misoprostol 50 µg insert for efficacy outcomes [24]. Across the two trials, the median time to vaginal delivery for women who received dinoprostone vaginal insert was 27.5–32.8 h (35.5–43.1 h for nulliparous women and 17.6–20.1 h for parous women) [24, 25]. The proportions of women who delivered by caesarean section for dinoprostone recipients was 27.1% in both trials [24, 25], which was not significantly different to the proportions of misoprostol 50 µg (28.9%) or misoprostol 100 µg (28.3%) recipients in MVI [24] or the proportion of misoprostol 200 µg recipients (26.0%) in EXPEDITE [25].

Other studies have investigated dinoprostone vaginal insert compared with titrated oral misoprostol solution (prepared by dissolving misoprostol tablets in water) for cervical ripening [30, 31]. In a multicentre open-label trial of 481 women indicated for labour induction, the mean time from treatment initiation to vaginal delivery was significantly ($p=0.04$) shorter for women who received dinoprostone vaginal insert compared with women who received titrated oral misoprostol solution (Table 2) [31]. A higher proportion of women in the dinoprostone vaginal insert group than the titrated oral misoprostol group delivered vaginally within 12 h (40.1 vs. 21.4%; $p=0.03$), but there was no difference between the two groups in the overall proportions of women who delivered vaginally (81.9 vs. 85.8%; $p=0.93$) [31]. In a separate trial of 160 women, vaginal delivery within 24 h was achieved in 44 (55.0%) of 80 women who received dinoprostone vaginal insert and 56 (70.0%) of 80 women

Table 2 Key efficacy outcomes in randomized controlled trials of dinoprostone vaginal insert versus misoprostol in cervical ripening and induction of labour[a]

Trial	*n*[b]	DVI (max. placement time)	MIS dosage details	First treatment to vaginal delivery (h)[c]		Vaginal delivery within 24 h (% of participants)		Caesarean section (% of participants)	
				DVI group	MIS group	DVI group	MIS group	DVI group	MIS group
Wing et al. [26]	200	24 h	25 µg p.v. q4 h (max. 6 doses)	22.7	21.6	45.9	51.5	20.4	18.2
Sanchez-Ramos et al. [27]	223	12 h	50 µg p.v. q3 h (max. 8 doses)	17.4[d]	11.6[d]**	60.9	71.3	13.0	22.2
Garry et al. [28]	200	24 h[e]	50 µg p.v. q3 h (max. 8 doses)	16.8	13.2*	38.2	68.0**	39.3	28.9
Bolnick et al. [29]	151	12 h[f]	25 µg p.v. q4 h (max. 6 doses)[g]	15.7	16.0	81.1	81.8	21.6	16.9
Rouzi et al. [30]	160	24 h	Titrated oral solution[h]	20.2	17.6	55.0	70.0	22.5	11.3
Wang et al. [31]	481	Not stated	Titrated oral solution[i]	15.7[†]	21.3	80.4	64.8	18.0	14.2

DVI dinoprostone 10 mg vaginal insert, *max.* maximum, *MIS* misoprostol, *p.v.* per vaginam, *qxh* every x hours

*$p < 0.05$, **$p < 0.001$ vs. DVI; †$p < 0.05$ vs. MIS

[a]To be included in the table, trials had ≥ 150 participants, were fully published and compared slow-release dinoprostone 10 mg vaginal insert versus misoprostol tablets administered p.v. or in a prepared oral solution

[b]Total number of participants randomized

[c]Values are means unless otherwise indicated

[d]Values are medians

[e]One 10 mg insert every 12 h for a maximum of 24 h

[f]Participants in the DVI group also received concurrent low-dose oxytocin

[g]In this group, MIS treatment was followed by high-dose oxytocin

[h]20 µg hourly for 2 doses, 30 µg hourly for 3 doses, 40 µg after 1 h (1 dose), 50 µg after 1 h (1 dose), then 60 µg hourly for 4 doses

[i]20 µg hourly for 2 doses, 30 µg hourly for 3 doses, 40 µg after 1 h (1 dose), 50 µg after 1.5 h (1 dose), then 60 µg 2-hourly for 2 doses

who received titrated oral misoprostol solution ($p = 0.05$) (Table 2) [30].

In a meta-analysis of 11 randomized controlled trials that compared dinoprostone vaginal insert with vaginal misoprostol tablets for cervical ripening [32], women who received dinoprostone vaginal insert ($n = 785$) were found to have a lower likelihood of vaginal delivery within 12 h [relative risk (RR) 0.65; 95% CI 0.44–0.96] or within 24 h (RR 0.83; 95% CI 0.74–0.94) than women who received vaginal misoprostol tablets ($n = 787$). Women treated with dinoprostone vaginal insert were also found to be more likely to require oxytocin augmentation (RR 1.45; 95% CI 1.20–1.74). There was no difference between the two groups in terms of the proportions of women who delivered by caesarean section (RR 1.01; 95% CI 0.85–1.19) [32].

A 2015 meta-analysis of 280 randomized controlled trials of prostaglandin-based methods for cervical ripening and labour induction found that high-dose (≥ 50 µg) vaginal misoprostol and low-dose (< 50 µg) titrated oral misoprostol solution were the first and second most effective methods for achieving a vaginal delivery within 24 h [33]. The favourability of high-dose vaginal misoprostol over dinoprostone vaginal insert in terms of the odds of achieving vaginal delivery within 24 h reached the conventional level of statistical significance in the network meta-analysis. Additionally, the analysis ranked dinoprostone vaginal insert above low-dose oral misoprostol tablets but below low-dose titrated oral misoprostol solution, low-dose vaginal misoprostol, high-dose oral misoprostol tablets and misoprostol vaginal insert, without reaching statistical significance for these comparisons [33].

3.3 Comparisons with Other Dinoprostone Formulations

Several, mostly small, randomized controlled trials have compared the efficacy of dinoprostone vaginal insert versus other formulations (and routes of administration) of dinoprostone in cervical ripening, including vaginal gel and tablets formulations and intracervical administration. A 2014 Cochrane review of vaginal prostaglandin for cervical ripening and labour induction concluded that there was no discernible difference in the effectiveness of dinoprostone vaginal insert compared with other dinoprostone formulations [34]. This conclusion is supported by three other meta-analyses, which found that dinoprostone vaginal insert was as effective as other dinoprostone formulations in key efficacy outcomes related to cervical ripening and labour

induction [33, 35, 36], although one of these analyses did find that the vaginal insert significantly ($p = 0.003$) increased the probability of achieving a vaginal delivery within 24 h compared with dinoprostone gel [odds ratio (OR) 2.35; 95% CI 1.34–4.13] [36]. Given that differences in effects between different formulations of the same agent would generally be expected to be small, it was not considered surprising that very limited differences between the effectiveness of different formulations of dinoprostone were found, particularly given the generally small size of the trials that have been conducted [34].

3.4 Comparisons with Mechanical Methods

In addition to the comparisons of dinoprostone vaginal insert with other pharmacological methods, the dinoprostone insert has been compared in randomized clinical trials versus mechanical methods for cervical ripening. The largest and best designed of these trials compared dinoprostone vaginal insert with use of Foley [37, 38] or double-balloon [39] catheters. Some differences in efficacy outcomes were observed (see below). However, likely due to differences in trial design (including inclusion criteria), the overall conclusions based on these trials are not clear.

One study of 397 women with an unfavourable cervix compared dinoprostone vaginal insert (maximum 24 h) with a transcervical Foley catheter left in place for up to 12 or 24 h [37]. The proportions of women who achieved vaginal delivery within 24 h (primary outcome) were higher in the groups that underwent cervical ripening with dinoprostone vaginal insert (48.5%) and Foley catheter for 12 h (59.8%) than in the 24-h Foley catheter group (21.0%; $p < 0.0001$ for both comparisons), but there was no statistical difference between the dinoprostone vaginal insert and 12-h Foley catheter groups ($p > 0.05$). There was no difference between the three groups in the proportions of women who delivered vaginally (all 66.7–69.9%) [37].

In a separate study ($n = 376$) comparing use of a Foley catheter (maximum, 12 h) versus dinoprostone vaginal insert (maximum, 12 h), cervical ripening with a Foley catheter was associated with a shorter median time to delivery (primary outcome; 21.6 vs. 26.6 h; $p = 0.003$) and a higher proportion of women achieving vaginal delivery within 24 h (44 vs. 30%; $p = 0.004$) [38].

In another study ($n = 210$), a greater proportion of women achieved vaginal delivery within 24 h when treated with a double-balloon catheter (maximum, 12 h) than with dinoprostone vaginal insert (maximum, 24 h) [68.6 vs. 49.5%; OR 2.22; 95% CI 1.26–3.91] [39].

A 2016 meta-analysis that compared dinoprostone vaginal insert with use of a Foley catheter found that the mean time from treatment initiation to delivery was significantly ($p = 0.01$) shorter for women who received dinoprostone vaginal insert, but there was no difference between the two methods in the percentage of women who delivered vaginally within 24 h [40]. Compared with Foley catheter, dinoprostone vaginal insert was associated with a significantly ($p < 0.01$) increased risk of excessive uterine activity, but there was no difference in the caesarean section rate or in neonatal outcomes [40].

Despite the inconclusive findings of these studies overall in terms of efficacy outcomes, guidelines generally recommend the use of a prostaglandin medication over the use of a mechanical method for cervical ripening (see Sect. 6).

4 Safety and Tolerability of Dinoprostone Vaginal Insert

Dinoprostone vaginal insert is well tolerated as an agent for cervical ripening and labour induction. As is observed for other methods of labour induction, the most significant adverse event associated with dinoprostone vaginal insert is uterine hyperstimulation. Adverse events such as drug-related fever, nausea, vomiting, diarrhoea and abdominal pain have been reported in < 1% of women who received dinoprostone vaginal insert [12]. Other adverse events that have been reported in postmarketing surveillance in women who received dinoprostone vaginal insert include hypersensitivity, disseminated intravascular coagulation, uterine rupture (including cases that required a hysterectomy and cases that resulted in foetal or neonatal death), hypotension and amniotic fluid embolism [12].

In the dinoprostone vaginal insert group of the EXPEDITE trial (see Sect. 3.2), adverse events were reported in 54.6, 21.2 and 58.1% of women or neonates in the intrapartum, postpartum and neonatal periods, respectively, with these proportions not significantly different to those reported in the misoprostol 200 µg vaginal insert group [25]. In contrast, intrapartum adverse events leading to insert retrieval occurred in significantly fewer women in the dinoprostone group compared with the misoprostol 200 µg group (4.0 vs. 11.4%; $p < 0.001$) [41]. Among women in the dinoprostone vaginal insert group, the most frequent adverse events leading to insert retrieval were category II or III FHR patterns (in 1.9% of women) and uterine tachysystole with FHR involvement (1.2%) [41]. The overall rates of category II and category III FHR patterns as adverse events in the dinoprostone vaginal insert group were 25.7 and 0.7%, respectively [25]. Uterine tachysystole requiring intervention occurred in significantly fewer women receiving dinoprostone vaginal insert than misoprostol 200 µg vaginal insert (4.0 vs. 13.4%; $p < 0.001$) [25]. In the MVI trial (Sect. 3.2), uterine tachysystole that was directly attributable to the study medication was observed in 14.9, 8.1 and 15.0% of women who received dinoprostone vaginal insert, misoprostol 50 µg

and misoprostol 100 μg vaginal inserts, respectively, with the incidence in the misoprostol 50 μg vaginal insert group significantly lower than in the other two groups [24]. Abnormal cardiotocographic events that occurred while the insert was in place were reported in 27.1% of dinoprostone vaginal insert recipients in the MVI study, with a median time to the first event of 5.5 h [42].

Overall, uterine hyperstimulation (with or without FHR changes) has been reported in 5–15% of women who were administered dinoprostone vaginal insert for cervical ripening in randomized controlled trials [43]. If uterine hyperstimulation occurs the insert should be removed (see Sect. 5), upon which hyperstimulation typically reverses within 15 min. In a placebo-controlled study of dinoprostone vaginal insert, five (4.9%) of 102 women in the active agent group [and no women in the placebo group ($n = 104$)] experienced uterine hyperstimulation (with three of the five cases having associated nonreassuring FHR tracings) [22]. Hyperstimulation reversed in 2–13 min of removal of the insert; one of these women required tocolytics [22]. In a 2015 pair-wise meta-analysis, dinoprostone vaginal insert was found to have an almost threefold decrease in the odds of uterine hyperstimulation compared with vaginal misoprostol ≥ 50 μg (OR 0.37) [33].

In addition to the good maternal tolerability of dinoprostone vaginal insert, there are no significant concerns regarding the safety of the agent for the neonates. Five-minute Apgar scores were ≥ 7 in 646 (98.2%) of 658 studied neonates whose mothers were administered dinoprostone vaginal insert [12].

5 Dosage and Administration of Dinoprostone Vaginal Insert

Dinoprostone 10 mg vaginal insert is approved in several countries of the EU (including the UK, France, Germany, Italy, Spain) [13], in the USA [12] and in a number of other countries worldwide for use in cervical ripening. Under the UK approval, dinoprostone vaginal insert is indicated for the initiation of cervical ripening in patients at term (from 37 completed weeks of gestation) [14]; in the USA, the approved indication is for the initiation and/or continuation of cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labour [12].

The dinoprostone vaginal insert consists of a drug delivery device held within a polyester pouch (which is attached to a long polyester tape for device removal) [12, 14]. Dinoprostone vaginal insert should only be used in a hospital setting where facilities for continuous foetal and uterine monitoring are available. For administration, the insert should be placed transversely in the posterior fornix of the vagina using, if required, a minimal amount of water-soluble lubricant to assist insertion. Following placement of the insert, the patient should remain recumbent for a period of time (20–30 min according to the UK summary of product characteristics [14]; 2 h according to the US prescribing information [12]) but may be ambulatory thereafter.

Whilst the insert is in place, uterine activity, foetal status and the progression of cervical dilation and effacement should be carefully monitored. The insert can be left in place for up to 12 [12] or 24 [14] h but should be removed if labour commences. Furthermore, the insert should be removed upon any evidence of uterine hyperstimulation, prolonged or excessive uterine contractions, foetal distress, or other foetal or maternal adverse reactions or complications. Since dinoprostone may potentiate the activity of oxytocic agents (see Sect. 2), it is also important that the dinoprostone vaginal insert is removed prior to the initiation of oxytocin administration [12, 14].

Dinoprostone vaginal insert is contraindicated in patients with unexplained vaginal bleeding during the pregnancy, or when strong prolonged uterine contractions may be detrimental to foetus safety or uterine integrity, such as in women who have previously undergone a caesarean section or other major uterine surgery [12, 14]. Caution should be exercised whenever dinoprostone vaginal insert is used in women aged ≥ 30 [12] or ≥ 35 [14] years, in women with complications during pregnancy or in those with a gestational age > 40 weeks since these factors are associated with an elevated risk for developing postpartum disseminated intravascular coagulation, which could potentially be further increased by pharmacological induction of labour [12, 14]. Caution should also be exercised when dinoprostone vaginal insert is used in patients with ruptured membranes, when there is a multiple pregnancy, or in patients with a history of glaucoma, asthma or uterine hypertony [12, 14].

Local prescribing information should be consulted for full details on the use of dinoprostone vaginal insert, including further information on contraindications, warnings and precautions.

6 Place of Dinoprostone Vaginal Insert in Cervical Ripening

Artificial initiation of labour is used in up to a quarter of deliveries, and the success of induction largely depends on the condition, or ripeness, of the cervix. In the absence of a naturally ripe or favourable cervix, there are numerous methods available to promote ripening [1, 2, 5, 8]. The choice of most appropriate method can depend on a variety of different factors, including maternal and obstetrical characteristics (e.g. cervix favourability/Bishop score, membrane status, parity, gestation period, indication for induction) and the

patient's individual needs and preferences. Pharmacoeconomic considerations may also influence treatment decisions [1].

The efficacy (Sect. 3) and safety (Sect. 4) of dinoprostone vaginal insert, the focus of this review, has been evaluated in numerous randomized trials. Although most individual trials were small in size, collectively the large body of evidence shows that dinoprostone vaginal insert is a safe and effective agent for the promotion of cervical ripening in patients with an unfavourable cervix at term. There was some variability observed between trials in data relating to the efficacy of the insert. For example, in the trials covered in Tables 1 and 2, the percentage of dinoprostone vaginal insert recipients who achieved a vaginal delivery in ≤ 24 h ranged from 34.0 to 81.1%. This variability is likely to be largely related to the heterogeneity of the study populations across trials, notably the differences in degrees of cervix unfavourability at baseline (based on Bishop scores). Factors that may be associated with an increased likelihood of successful cervical ripening and labour induction with dinoprostone vaginal insert include multiparity, maternal age < 35 years, maternal body mass index < 30 and a higher Bishop score or cervical dilation at baseline [44, 45].

Dinoprostone vaginal insert is superior to placebo (Sect. 3.1) and generally comparable to other prostaglandin methods [i.e. other dinoprostone formulations (Sect. 3.3), or misoprostol (Sect. 3.2)] for key efficacy outcomes in cervical ripening. The agent is well tolerated, with a generally favourable safety profile, both maternal and foetal/neonatal (Sect. 4). As with all prostaglandin agents used in cervical ripening, the main adverse event associated with dinoprostone vaginal insert is uterine hyperstimulation, which has been observed in approximately 5–15% of women who were administered the agent [43]. However, this is generally rapidly reversible upon removal of the insert (Sect. 4).

Dinoprostone vaginal insert and other dinoprostone formulations appear to be equally effective at promoting cervical ripening, with no substantial differences in efficacy outcomes between the different formulations, based on available evidence (Sect. 3.3). The main advantage of the dinoprostone vaginal insert over other dinoprostone formulations is the ability, through removal of the device, to easily stop the dosing at the onset of labour or in the event of uterine hyperstimulation (or other adverse events) [43]. Another potential advantage of the vaginal insert is the nature of the controlled release of dinoprostone (Sect. 2), which may lead to a more progressive induction of cervical ripening and labour [43]. This, for many patients, may be preferable to an excessively rapid onset of contractions that can occur with some other methods.

In comparisons between dinoprostone vaginal insert and misoprostol formulations, small differences in measures of efficacy and safety appear to be largely dependent on the misoprostol dosage (Sects. 3.2 and 4). At higher dosages, misoprostol appears to have an advantage in some efficacy outcomes, most notably the time from treatment initiation to vaginal delivery. However, there appears to be a trade-off between improved efficacy outcomes and an increased risk of adverse events such as uterine hyperstimulation or tachysystole at higher misoprostol dosages. For example, in two large trials, while dinoprostone vaginal insert had similar efficacy and safety to a misoprostol 100 µg vaginal insert, a misoprostol 200 µg vaginal insert was more effective across most measured outcomes but was also associated with a higher incidence of uterine tachysystole requiring intervention (Sects. 3.2 and 4). Dinoprostone and misoprostol vaginal inserts both have the benefits associated with a controlled-release device, including the advantages of a single application and easy removal to limit dosing when required.

According to a large 2015 meta-analysis, use of high dose (≥ 50 µg) vaginal misoprostol tablets was the most effective prostaglandin-based cervical ripening method for achieving a vaginal delivery within 24 h (Sect. 3.2), a key efficacy outcome for evaluating cervical ripening success. Use of misoprostol tablets (by vaginal or oral administration) is also considered an inexpensive option for cervical ripening. However, it should be noted that their use in cervical ripening remains off-label in many countries.

In general, guidelines recommend the use of a prostaglandin medication (if available and not contraindicated) for cervical ripening over the use of a mechanical method, while recognizing that mechanical methods are generally still effective [1, 2, 5, 8]. Mechanical methods are also generally inexpensive and have no special requirements for preservation. A potential disadvantage of some cervical ripening mechanical methods (e.g. Foley catheter) is that their application may be more difficult or technically challenging than use of pharmacological agents [46]. In addition, there have been concerns that the introduction of a mechanical device into the uterus is likely to increase the risk of infection, as could frequent vaginal manipulations. There is some evidence that mechanical methods may increase the risk of infection compared with pharmacological agents [47]; however, available data on the comparative risks with different methods are scarce and difficult to interpret.

In summary, data show that dinoprostone vaginal insert is a safe and effective method for initiating cervical ripening in patients with an unfavourable cervix at term. The device's retrieval system enables dose control by facilitating easy removal of the insert at the onset of labour, or in the event of adverse events such as uterine hyperstimulation. No trials have been conducted in women with a multiple pregnancy and data are limited for women with ruptured membranes so dinoprostone vaginal insert should be used with caution in such women. However, overall, clinical trials

on dinoprostone vaginal insert have included women with a wide range of maternal and obstetrical characteristics and indications for induction. In conclusion, the demonstrated effectiveness and safety of the device, combined with the benefits of controlled drug release from a simple, single application, and efficient dose control, suggest that dinoprostone vaginal insert is a valuable option for promoting cervical ripening in patients with an unfavourable cervix at term.

Data Selection Dinoprostone: 471 records identified	
Duplicates removed	113
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	194
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	117
Cited efficacy/tolerability articles	22
Cited articles not efficacy/tolerability	25
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Dinoprostone, Cervidil, Propess, FE999901, Prostaglandin-E2 Records were limited to those in English language. Searches last updated 01 October 2018	

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Compliance with Ethical Standards

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