

PRODUCT MONOGRAPH

PROSTIN® E₂ Vaginal Gel

dinoprostone vaginal gel

1 mg per 3 gram (syringe)

2 mg per 3 gram (syringe)

Prostaglandin

Pfizer Canada Inc
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THERAPEUTIC CLASSIFICATION

Prostaglandin

ACTION, CLINICAL PHARMACOLOGY

Dinoprostone is a synthetic analogue of Prostaglandin E₂ (PGE₂). The major clinical application of PGE₂ relates to its effect on uterine smooth muscle. This property has led to its obstetrical use for term labour induction and preterm evacuation of uterine contents (for fetal death *in utero*, hydatidiform mole, and abortion). Similarly, this effect on other smooth muscle beds results in prominent dose-related side effects of nausea, vomiting, and abdominal cramping. It also acts as a vasodilator and may be associated with modest hypotension. Changes that occur in the cervix during pharmacologically induced softening, effacement, and dilatation (collectively referred to as cervical ripening) appear to involve more than smooth muscle contraction. While a small amount of smooth muscle is found in this structure, the body of the cervix is composed mainly of fibrous connective tissue and surrounding collagenous matrix.

Although the exact mechanisms are not fully understood, it is theorized that the pharmacologic action of PGE₂ is related to its ability to regulate intracellular cyclic 3', 5'-adenosine monophosphate (cAMP) levels and cellular membrane calcium ion transport. In many tissues, PGE₂ appears to stimulate the syntheses of cAMP by activating the enzyme, adenylate cyclase. It has been proposed that the prostaglandins are released by hormonal stimulation and, in turn, stimulate the enzyme. It should be noted, however, that some effects of prostaglandins are independent of cAMP and are mediated through that of cGMP.

In controlled clinical trials of 964 patients (484 on PROSTIN E₂ vaginal gel; 480 on oxytocin), 67% of PGE₂ treated patients and 67% of oxytocin treated patients had achieved satisfactory labour at 12 hours while 69% of PGE₂ treated patients and 68% of oxytocin treated patients were successfully induced. There was a trend toward fewer cesarean sections in the PGE₂ treated group.

INDICATIONS AND CLINICAL USE

PROSTIN E₂ vaginal gel (dinoprostone) is indicated for the induction of labour in term or near term pregnant women who have favourable induction features, a singleton pregnancy and a vertex presentation.

CONTRAINDICATIONS

PROSTIN E₂ vaginal gel (dinoprostone) should not be used in patients with known hypersensitivity to dinoprostone or any other constituents of the gel (colloidal silicon dioxide and triacetin).

Labour should not be induced in patients who have any of the following:

1. Patients in whom oxytocic drugs are generally contraindicated or where prolonged contractions of the uterus are considered inappropriate. These include the following situations:
 - a. Patients with a history of cesarean section or major uterine surgery;
 - b. Patients with cephalopelvic disproportion;
 - c. Patients with a history of difficult labour and/or traumatic delivery;
 - d. Grand multiparae with six or more previous term pregnancies;
 - e. Patients with suspected or clinically evident pre-existing fetal distress;
 - f. Patients with overdistention of the uterus (multiple pregnancy, polyhydramnios);
 - g. patients with pre-existing uterine hypertonus;
 - h. circumstances that make it impossible for a responsible physician to be present.
2. Patients with ruptured amniotic membranes or suspected choriamnionitis;
3. Engagement of the head has not taken place;
4. Patients with unexplained vaginal bleeding during this pregnancy;
5. Patients with fetal malpresentation;
6. Patients with gynecological, obstetrical or medical conditions that preclude vaginal delivery.
7. Patients whose pregnancy is complicated by an abnormal position of the placenta or umbilical cord.
8. Patients with a past history of, or existing pelvic inflammatory disease, unless adequate prior treatment has been instituted;
9. Patients with active cardiac, pulmonary, renal or hepatic disease.

PROSTIN E₂ vaginal gel should not be used simultaneously with other oxytocics (see Warnings).

WARNINGS

PROSTIN E₂ vaginal gel (dinoprostone) like other effective oxytocic agents, should be used with strict adherence to recommended dosages, by medically trained personnel in hospital surroundings with appropriate obstetrical care facilities.

The sequential use of oxytocin less than twelve hours following PROSTIN E₂ vaginal gel has not been carried out. Therefore, infusion of oxytocin should not be started until 12 – 24 hours has elapsed following the use of PROSTIN E₂ vaginal gel.

Reports of epileptic seizures with other forms of prostaglandins have been published. The association of prostaglandin with seizures has not been conclusively proven. One epileptic patient under poor control, when treated with PROSTIN E₂ tablets, did experience a grand mal seizure. Therefore, it is recommended that PROSTIN E₂ vaginal gel be used in known epileptics only when their epilepsy is under good control and then only with maximum care and observation on the part of the physician in charge. Elective induction of labor should not be employed in these patients.

Women aged 35 years or older, those with complications during pregnancy including severe preeclampsia and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labor induction (see section **ADVERSE REACTIONS**). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum period.

The Health Professional should be alert that the intracervical placement of dinoprostone gel may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

PRECAUTIONS

Prior to and during the use of labour inducing agents including PROSTIN E₂ vaginal gel (dinoprostone), uterine activity, fetal status and the character of the cervix (dilation and effacement) should be carefully monitored to detect possible evidence of undesired responses. These include hypertonus, sustained uterine contractility or fetal distress. As with other effective oxytocic agents, it is recommended, during labour induction with PROSTIN E₂ vaginal gel, that continuous electronic monitoring of uterine activity and fetal heart rate be employed; particularly in cases where there is a known history of hypertonic uterine contractility or tetanic uterine contractions.

Cephalopelvic relationships should be carefully evaluated before the use of labour inducing agents, including PROSTIN E₂ vaginal gel.

PROSTIN E₂ vaginal gel for labour induction should be used with caution in patients with compromised cardiovascular, hepatic or renal function and in patients with asthma or glaucoma.

Prostaglandins are excreted in human milk. Supportive data on the effect on infants are still inconclusive.

PROSTIN E₂ vaginal gel is an intravaginal product. Not to be used intracervically. Placement of prostaglandin-containing gel into the extra-amniotic space has been associated with uterine hyperstimulation.

Consistent with treatment with any labour inducing agent, patients who develop uterine hypertonus or hypercontractility or in whom nonreassuring fetal heart patterns develop should be managed in a manner that addresses the welfare of the fetus and mother.

As with any oxytocic agent, the possibility of uterine rupture and/or cervical laceration should be considered in the presence of excessive uterine activity or unusual uterine pain, or where high-tone myometrial contractions are sustained.

In approximately 54% of 484 patients treated in controlled clinical trials with PROSTIN E₂ vaginal gel for labour induction, the membranes were artificially ruptured after administration of the gel.

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce proliferation of bone. Such effects have also been noted in newborn infants who have received prostaglandin E₁ during prolonged treatment. There is no evidence that short term administration of PROSTIN E₂ can cause similar bone effect.

Drug Interactions:

PROSTIN E₂ vaginal gel, like all prostaglandins, may potentiate the uterine response to oxytocin. Patients requiring oxytocin induction, after pre-induction cervical ripening with PROSTIN E₂, should be carefully monitored. (See WARNINGS)”

ADVERSE REACTIONS

In clinical trials of 965 patients treated with PROSTIN E₂ vaginal gel (dinoprostone) compared to placebo (26 patients) and oxytocin (739 patients), the following profile of events was observed:

Pooled events N(%)			
	Placebo N=26	PGE₂ N=965	Oxytocin N=739
fetal distress	1 (3.9)	42 (4.4)	37 (5.0)
failure to progress	2 (7.7)	12 (1.2)	14 (1.9)
failed induction		15 (1.6)	14 (1.9)
hypercontractility		30 (3.1)	29 (3.9)
fetal heart rate abnormalities		82 (8.5)	77 (10.4)

Maternal Adverse Events: The following maternal adverse events have been reported with use of the vaginal gel:

Gastrointestinal disorders: Diarrhea, nausea, vomiting

General disorders and administration site conditions: Fever

Immune system disorders: Hypersensitivity reactions (e.g. Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction)

Musculoskeletal and connective tissue disorders: Back pain

Pregnancy, puerperium and perinatal conditions: Uterine contractile abnormalities (increase frequency, tone, or duration), uterine rupture

Reproductive system and breast disorders: Warm feeling in vagina

Cardiac disorders: cardiac arrest

Fetal Adverse Events: The following fetal adverse events have been reported with the use of the vaginal gel:

Investigations: Fetal distress/altered fetal heart rate (FHR) including bradycardia

Pregnancy, puerperium and perinatal conditions: Still births

Post-Marketing Adverse Drug Reaction:

Blood and lymphatic system disorders: Disseminated intravascular coagulation

OVERDOSE

Overdosage with PROSTIN E2 GEL may be expressed by uterine hypercontractility and uterine hypertonus. Because of the transient nature of PGE₂-induced myometrial hyperstimulation, nonspecific, conservative management was found to be effective in the vast majority of the cases; i.e., maternal position change and administration of oxygen to the mother. β -adrenergic drugs may be used as a treatment of hyperstimulation following the administration of PGE₂ for cervical ripening.

DOSAGE AND ADMINISTRATION

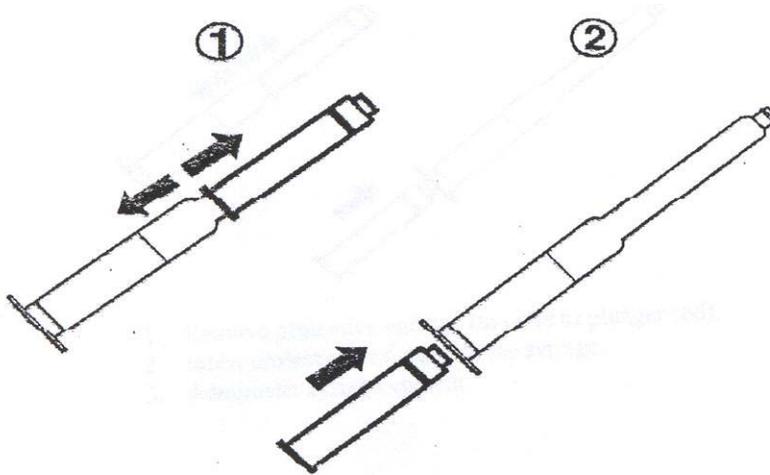
For intravaginal use only. Not to be used intracervically.

For the induction of labour in term or near term pregnant women who have favourable induction features, a singleton pregnancy and a vertex presentation: An initial dose of 1mg PROSTIN E₂ vaginal gel (dinoprostone) placed into the posterior fornix of the vaginal canal is recommended. A dose of 1 mg or 2 mg of PROSTIN E₂ vaginal gel may be repeated, once, 6 hours later depending upon the patient's response to the initial dose.

Patients should remain in a lateral or supine position for 30 minutes after administration to prevent leakage of the gel.

PROSTIN E₂ vaginal gel prefilled syringes contain overfill and are designed to deliver a dose of 1 mg or 2 mg dinoprostone.

The syringe should be assembled by following the sequence in the diagram.



1. Remove protective end cap (to serve as plunger rod).
2. Insert protective end cap into the syringe.
3. Administer syringe content.

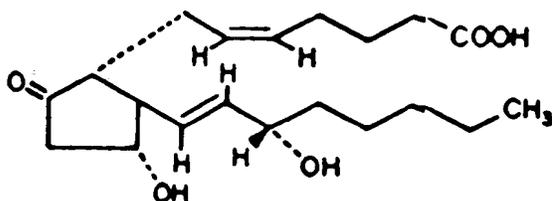
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Dinoprostone

Chemical Name: (5Z,11 α ,13E,15S)-11,15-dihydroxy-9-oxoprostano-5,13-dien-1-oic acid

Structural Formula:



Molecular Formula: C₂₀H₃₂O₅

Molecular Weight: 352.5

Description: Dinoprostone is a white crystalline powder. It has a melting point range of 64°C to 71°C. Dinoprostone is readily soluble in the triacetin component of the gel formulation. It is also soluble in ethanol and in 25% ethanol in water. Solubility in water is limited to 130 mg/100 mL.

Stability and Storage Recommendations:

PROSTIN E₂ vaginal gel has a shelf life of 24 months when stored at 2 - 8°C, under continuous refrigeration.

AVAILABILITY OF DOSAGE FORMS

PROSTIN E₂ vaginal gel (dinoprostone) is supplied as a semi-translucent viscous gel in a single dose container/closure system. Each syringe contains

Medicinal ingredient: dinoprostone (PGE₂) 1.0 mg or 2.0 mg per 3.0 grams (2.5 mL).

Non medicinal ingredients: colloidal silicon dioxide and triacetin

The contents of one syringe to be used for one patient. Discard after use.

PHARMACOLOGY

Pregnancy has been interrupted in hamsters, mice, rats and Rhesus monkeys by administering dinoprostone. Some skeletal abnormalities were also observed in rats when dinoprostone was administered to the mother on days 9, 10 and 11 of gestation. In a similar study, in rabbits, this effect was not observed.

Also, pseudo-pregnancy was shortened in rats, and uterine motility stimulated in Rhesus monkeys. Cervical diameter, weight or glycogen content were not altered in rats treated with dinoprostone.

Dinoprostone was injected subcutaneously into two groups of 5 hamsters (*Mesocricetus auratus*) each, (plus a control group of 8 hamsters), as a single injection on day 4 of pregnancy. On day 7, 0 of 5, 2 of 5 and 8 of 8 animals were pregnant in groups injected with 0.5 mg dinoprostone, 0.25 mg dinoprostone or saline respectively. Some depression of normal activity was noted following prostaglandin injection. Dinoprostone was injected intravenously into 2 groups of mice; pregnant and nonpregnant, at a dose of 30 mg/kg. This dosage was nontoxic to the nonpregnant mice. It caused fetal death in the pregnant mice.

Dinoprostone was injected subcutaneously into rats (2 mg/rat/day) on days 4, 5 and 6 of pregnancy. Only 1 out of 6 animals was pregnant on day 10. Dinoprostone injected subcutaneously (1 mg/rat) shortened pseudo-pregnancy from 17 days (control animals) to 10 days (treated animals) when injected b.i.d. on days 4 through 7 of pseudo-pregnancy. Dose levels in excess of 2 mg/day were found to be toxic and/or fatal to rats. Dinoprostone infused into rats through an indwelling subcutaneous catheter at a rate of 10 mg/kg/day for 48 hours starting on day 5 of pregnancy, reduced pregnancy rate from 87% (control) to 17% (treated) by day 10 or 11.

Dinoprostone was injected subcutaneously into two groups of rats (0.25 mg/day and 0.5 mg/day) on days 9, 10, and 11 of gestation. In the 0.5 mg groups, maternal weight decreased, litter weight and size also decreased and an increase in the number of resorption sites was observed. In some cases, the skeletal abnormalities were due to a teratogenic effect.

Intravenous infusions of dinoprostone, 0.8 µg/min., stimulated maximal uterine contractions in pregnant Rhesus (*Macaca Mulatta*) monkeys. Subcutaneous injections of 15 mg b.i.d. starting on day 34 (3 injections) terminated pregnancy, but injections initiated on day 42 did not. One vaginal application or subcutaneous injection of 2.0 mg of dinoprostone stimulated uterine contractility for 3 to 4 hours in Rhesus monkeys treated at day 120 - 125 of pregnancy. One vaginal application of 5.0 mg of dinoprostone stimulated uterine contractility for 5 hours. One intracervical application of 0.5 mg of dinoprostone stimulated uterine contractility for 5 hours.

Adult, virgin, estrogen-primed rats were injected subcutaneously with dinoprostone at a dose of 1.0 mg/animal. Relaxin increased the wet weight, volume and glycogen content of the uterus and uterine cervix. Dinoprostone did not affect any of these parameters, nor did it modify the action of relaxin on them. In addition, dinoprostone did not alter the inner circumference of the uterine cervix as did relaxin.

Studies of Effect on the Central Nervous System:

Prostaglandins are natural constituents of nervous tissue and are released from the brain following stimulation of afferent pathways. The literature is not extensive but does suggest that they may play a role of modulators. Studies have shown that the phosphodiesterase activity in mouse brain synaptic vesicles was inhibited by 58% at dinoprostone concentration of 1×10^{-3} M. The significance of these findings is not known. In rats, dinoprostone has been shown not to alter the utilization or turnover of catecholamines in the brain. The role of prostaglandins in the central nervous system and their interaction with the sympathetic nervous system is not clear.

Studies of Effect on the Cardiovascular System:

Dinoprostone decreases mean arterial blood pressure, increases cardiac output and decreases peripheral resistance when administered intravenously to trained unanesthetized dogs. The effect appears to be primarily due to peripheral vasodilatation. This compound has a pressor effect in both rats and dogs that have been: pentobarbital anesthetized; vagotomized or pentolinium treated. In the dog, sensitivity is increased by 20 fold in the treated animals as compared with unanesthetized groups whereas in rats, the sensitivity is increased about 2 fold. The anesthetized, blocked dogs are more sensitive to prostaglandins than are similarly treated rats. Studies with albumin-bound and free dinoprostone show no difference in the depressor effect in rats when these preparations are administered by either the intravenous or intra-arterial route.

Dinoprostone is inactive, when administered subcutaneously at 0.1 and 0.2 mg/kg/day x 14 days, to stable renal hypertensive rats. It is effective in lowering the blood pressure of the Rhesus monkey when administered as a single IV dose of 20 or 40 μ g or as a continuous intravenous infusion of 8 μ g/min. In this species the infusion rate required to alter blood pressure was about 10 times greater than the minimal rate required to initiate uterine contractions in pregnant animals.

Dinoprostone tested *in vitro* at concentrations of 0.125 mg/ml had no hemolytic effect and did not cause any increase in osmotic fragility of human whole red blood cells.

Studies of Effect on the Respiratory System:

Contrary to the vasodilation effects seen with dinoprostone in the blood pressure studies, the reverse effect is obtained in terms of nasal patency. In anesthetized dogs with the trachea cannulated, injections of dinoprostone into the ipsilateral carotid artery results in an increased nasal patency.

In an *in vitro* system using tracheal muscle from the guinea pig, dinoprostone is effective in reversing the muscle contractions induced by SRS-A (slow reacting substance in anaphylaxis).

Studies of Effect on the Gastrointestinal System:

Dinoprostone administered by intravenous infusion, inhibits gastric secretion in dogs stimulated by either histamine hydrochloride or food. The dose affording 50% inhibition of secretion under

these conditions is 0.75 µg/kg/min. In rats, continuous infusion of dinoprostone by the subcutaneous route, inhibits duodenal ulcer production by secretagogues. The ulcer inducing secretagogues used in these experiments were histamine plus carbachol; pentagastrin plus carbachol; histamine plus pentagastrin.

Dinoprostone is an effective stimulator of both rabbit duodenum and guinea pig ileum, as well as the gerbil colon, when tested in suitable *in vitro* systems. Albumin added to solutions of dinoprostone at concentrations of 20 mg/mL, inhibits its action on gerbil colon.

In the mouse, intra-peritoneal injection of dinoprostone stimulates smooth muscle as evidenced by defecation of the animals within 15 minutes. Using fecal weight as an end-point, concentrations of dinoprostone as low as 0.8 µg/kg can be detected. Repeated dosage with this compound under the test conditions described above causes frank diarrhea in the test animals.

Studies of Effect on Bone:

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce proliferation of bone.

Miscellaneous pharmacologic activities considered pertinent to efficacy and safety:

Dinoprostone inhibits ADP - and calcium-induced platelet aggregation in citrated PRP (Platelet Rich Plasma) from rat, rabbit and man. Dinoprostone is most effective when tested against the ADP induced aggregation of rabbit platelets. While this inhibition of rabbit platelet aggregation was seen at dinoprostone concentrations of 10 µg/ml and higher, lower concentrations, i.e. 3.0 to 0.1 µg/ml caused slight potentiation of the aggregation. This slight potentiating effect was, however, seen only when the ADP concentration was in a specific range of 0.5 to 1.0 µg/mL. This potentiation was not seen with rat or human platelets and must be considered a species specific phenomenon of questionable significance at this time.

Dinoprostone given twice daily by subcutaneous administration at high pharmacologic doses (0.5 to 2.0 mg/kg) during the induction phase of the disease, inhibits adjuvant induced arthritis in the rat. It is not effective in rats with well established disease. At the high doses used, evidence of adrenal hyperplasia, decrease in spleen weights, thymolysis and some weight loss as well as diarrhea were seen. Since the anti-inflammatory effect was seen only at high doses, the effect was considered non-specific.

Contrary to the above studies, dinoprostone does have some pro-inflammatory properties when injected into the hind paw of rats. The role of dinoprostone and prostaglandins in general in the phenomenon of inflammation remains to be established.

Metabolism:

Animal Studies:

In the rat and Rhesus monkey, intravenously administered dinoprostone and/or its metabolites are rapidly removed from the circulation. In the rat, 45 seconds after dosing with tritium labelled

dinoprostone, only 20% of the radioactivity remained in the blood, of which less than 3% of the dose was dinoprostone. In female Rhesus monkeys, 20 minutes after dosing with 17, 18-³H₂ dinoprostone, 5% of the radioactivity remained in the blood, decreasing to 1.5% of the dose after 70 minutes.

Quantitative studies of the absorption and excretion of radioactively labelled dinoprostone have been conducted in female rats following intravenous, oral, intrauterine, and intravaginal administration. The results indicated that the pattern of urinary and fecal excretion was independent of the route of administration, thus indicating both rapid and complete absorption.

Absorption of tritium labelled dinoprostone from the rat intestine *in vitro* has been studied utilizing ligated segments and a perfusion technique. Results indicate that:

1. Absorption is rapid. Transport of radioactivity out of the proximal portion, the distal portion, or the perfused intestine occurred with half-lives of 30 minutes, 80 minutes, and 30-40 minutes, respectively.
2. Distribution and metabolism are rapid and extensive. Maximum blood levels of radioactivity and of dinoprostone were 2-3% and 0.03 - 0.1% of the dose, respectively, after 30-60 minutes (compared to 3% and 0.6%, respectively, after subcutaneous administration).
3. Considerable metabolism occurs in the intestine prior to absorption (e.g. 50% of the radioactivity in the intestine after a 30-minute perfusion was intact dinoprostone). 15-Hydroxyprostaglandin-dihydrogenase was eluted into the lumen during perfusion.
4. Presence of protein (bovine serum albumin) or lipids in the intestinal perfusion did not inhibit absorption.

The absorption and excretion of dinoprostone radioactivity in female Rhesus monkeys after intravenous, oral and intravaginal administration have been studied. After oral administration, 63% of the radioactivity was excreted in the urine as compared with 84% following intravenous administration. Only 24.5% of the radioactivity was found in the urine following intravaginal administration with the maximum blood level attained being only 0.9% of the dose. This latter urinary excretion value may not be strictly comparable to the percentages obtained after oral and intravenous administration since a recovery balance was not included in the study.

Dinoprostone applied topically to hairless mice, in absolute ethanol or dimethylacetamide vehicles was rapidly absorbed and the radioactivity excretion pattern was comparable to that obtained in rats after systemic drug administration.

Urinary excretion represents the major route of elimination of drug-related products. In rats and monkeys, excretion is rapid and nearly complete 24 hours after oral or intravenous drug administration. Following intravenous administration, the extent of biliary excretion and subsequent elimination in the feces varies from 34% of the dose in rats to 7% in monkeys. Fecal excretion after oral administration was not significantly different in the rat, but increased to 24% of the dose in female monkeys.

Maximum tissue levels of labelled dinoprostone, primarily in the liver, kidney and lungs, are obtained within 30-60 minutes after dosing rats. After 24 hours less than 0.1% of the dose remains in any of the tissues measured except for the lower small intestine and large intestine.

CLINICAL PHARMACOLOGY

PROSTIN E₂ vaginal gel (dinoprostone) 0.5 mg administered endocervically facilitates preinduction cervical softening (cervical maturation) in patients with unfavorable induction features. The specific mechanism of action is not fully defined. However, experimental data in humans demonstrate that PGE₂ affects cervical hemodynamics thus leading to cervical maturation.

Dinoprostone stimulates the myometrium of the gravid uterus to contract in a manner that is similar to the contractions observed in the term uterus during spontaneous labour.

Clinically, preinduction treatment with PGE₂ Gel - 0.5mg resulted in successful labour induction in 83% of treated patients compared to 58% of non-gel controls. In addition, gel pretreatment resulted in a shorter mean induction-delivery interval of 10.2 hours compared to 11.6 hours for controls and a reduction in the cesarean section rate (28% compared to 34% for controls).

Notable side effects observed in a placebo controlled multicenter clinical trial with 397 patients consisted of

- (1) a 2.5% incidence of uterine contractile abnormalities in PGE₂ gel treated patients compared to 3.1% for controls;
- (2) an incidence of intrapartum fetal heart rate changes during or subsequent to PGE₂ gel administration in 8.4% of treated patients versus 3.6% of controls; and
- (3) vomiting and/or diarrhea occurred in 1.5% and 1.0% of treated and control patients, respectively. None of the side effects reported were considered a deterrent to the use of endocervical PGE₂ gel for preinduction cervical softening.

In both laboratory animals and man, large doses of PGE₂ can lower blood pressure, probably as a consequence of its effect on smooth muscle of the vascular system, and transient elevations of body temperature have been observed. PGE₂ is also capable of stimulating the smooth muscle of the gastrointestinal tract. This property may be responsible for the vomiting and/or diarrhea that is sometimes associated with the use of PGE₂.

Intravenously administered dinoprostone is extremely rapidly distributed and metabolized in humans. Only 3.2% of the administered dose remains in the blood as unchanged drug within 1.5 minutes. However, metabolites of dinoprostone have been identified in human blood and urine. The metabolites have lower pharmacological activity than the parent compound. However, the concentration of the metabolite in plasma is useful in evaluating the absorption of the drug. The metabolite, 11-deoxy-13,14-dihydro-15-keto-13-11 β -16-cyclo PGE₂, or bicyclo PGEM, was

studied in patients undergoing preinduction cervical softening with dinoprostone and in controls. The plasma concentrations of the bicyclo PGEM in patients not responding to dinoprostone were 18% higher than in controls. In patients responding to dinoprostone, the plasma concentration of bicyclo PGEM were 80% higher than in controls. Patients responding to dinoprostone had plasma bicyclo PGEM concentrations 140% higher than nonresponders. PGE₂ is 73% bound to human plasma albumin as determined by equilibrium dialysis.

PGE₂ is rapidly metabolized in the lungs, kidneys, spleen and liver. A single pass of an injected PGE₂ dose in the circulatory system converts 90% of PGE₂ to metabolites.

Dinoprostone is eliminated from the peripheral circulation rapidly with a half-life of less than 1 minute. In humans, 3 metabolites have been detected in the plasma and 8 metabolites have been detected in the urine.

After an intravenous dose of radiolabelled PGE₂, 50% of the injected radioactivity was recovered in the urine in two hours and 67% was recovered in 12 hours.

TOXICOLOGY

Acute Toxicity:

The LD₅₀ values for single dose dinoprostone administration are summarized below:

<u>SPECIES</u>	<u>ROUTE</u>	<u>LD₅₀</u> <u>(mg/kg)</u>	<u>OTHER</u>
Mouse	Intravenous	158	-
Mouse	Oral	500	-
Rat	Intravenous	45	-
Rat	Oral	513	-
Mouse	Intravenous		Not Toxic at 30 mg/kg Caused Fetal Death
Monkey	Intramyometrial		1.25mg Mild to Severe Coagulation Necrosis

Subacute Toxicity:

Dinoprostone was administered to rats, rabbits and dogs. Various dosages and routes of administration were studied. Rats tolerated 7.5 µg/kg/min. for 2 hours daily intravenously for 5 days, 5 mg/kg/day orally for 5 days and up to 18 mg/kg/day subcutaneously for 5 days. Rats tolerated 1.4 mg of dinoprostone administered in suppository form intravaginally for 6 days. It was nonirritating. However, a dosage of 5.7 mg was lethal to 2 of 10 rats. The administration of dinoprostone, 1 mg/day for 5 days, was nonirritating.

Rabbits tolerated dinoprostone in a triacetin gel base administered intravaginally for 7 days without irritation. At high doses, 8.10 and 10.80 mg/kg, clinical toxicity was observed and included diarrhea and mortality.

Dogs tolerated dinoprostone for 5 days when administered orally at a dose of 5 mg/kg/day or intravenously at a dose of 7.5 µg/kg for 2 hours daily.

Chronic Toxicity:

Dinoprostone was administered chronically to rats, dogs and monkeys.

Dinoprostone was administered intravenously to rats at a dose of 0.3 mg/kg/day for 10 days. Two of 12 rats died on days 4 and 5. No indications of toxicity were observed in the remaining 10 rats.

In another experiment, dinoprostone was administered intravenously to rats at a dose of 1.5 mg/kg for 2 weeks and considered to be nontoxic in this experiment. Dinoprostone was administered orally to rats for 14 days. The maximum tolerated dose was 100 mg/kg/day.

A dose of 320 mg/kg/day was toxic and lethal. Diarrhea, weight loss and increased stomach weights were noted. There were dose-related increases in the total surface area and in the surface areas of the nonglandular, fundic and pyloric mucosa. The height and volume of the fundic and pyloric mucosa were significantly increased at all dosage levels (10 - 320 mg/kg/day). Changes in the nonglandular stomach were not consistent and less severe, and were more prevalent in female rats.

Dinoprostone was administered topically to the abraded and unabraded skin of rats for 21 days. It was nonirritating to normal skin. It did not repress the rate of healing of abraded skin. No signs of systemic toxicity were observed.

Dinoprostone was administered subcutaneously to rats at doses of 2 to 12.5 mg/kg/day for 1 month. No serious drug-related changes were observed.

Dinoprostone was administered orally to rats at doses from 10 to 100 mg/kg/day for 3 months. Loosening of the feces was observed in rats given the 10 mg/kg/day dose and diarrhea was observed in rats given 100 mg/kg/day. Increases in stomach weight were observed at all dosage levels which were reversible within 3 months after cessation of dosing. Four of 30 male rats treated with 100 mg/kg died of uremia that appeared to be caused by urinary tract obstruction. These rats had a severe necrohemorrhagic urocystitis, acute prostatitis and hydronephrosis. Dose-related acanthotic squamous glandular junction and thickened glandular gastric mucosal epithelium was noted. In this study, the maximum tolerated dose of dinoprostone in Fisher 344 rats was 30 mg/kg.

Dinoprostone administered intravenously at a dose of 0.03 mg/kg/day was nontoxic in dogs.

Dinoprostone was administered orally to dogs at doses of 0.2 to 60.0 mg/kg/day for 1 to 3 days. After a 12 day withdrawal period, 6 and 20 mg/kg/day were administered to two groups. The maximum tolerated dose was between 6 and 20 mg/kg/day. The 6 mg/kg/day dose produced occasional vomiting and soft stools, but was otherwise well tolerated both acutely and chronically. The 20 mg/kg/day dose was poorly tolerated but not lethal. The 60 mg/kg/day dose was above the maximum tolerated dose. At doses of 20 mg/kg/day and higher, repeated vomiting, diarrhea, weight loss, serum and urinary electrolyte loss, dehydration, decreased pulse, decreased activity, CNS depression, injected sclera, lacrimation and ptyalism were observed. At all dosage levels, the fundic and pyloric mucosa were thickened, had a cobblestone appearance and increased gastric mucus was observed.

Dinoprostone was administered by continuous intravenous infusion at a rate of 1.5 mg/kg/day to monkeys for 2 weeks. It was found to be nontoxic.

Dinoprostone was administered intramuscularly to monkeys at doses from 0.25 to 1.0 mg/kg/day for 32 to 33 days. No evidence of toxicity was observed in this study.

Carcinogenicity:

Studies designed to show carcinogenic potential or lack of potential were not undertaken for dinoprostone. Since it is proposed for short term use, these studies were judged not appropriate for analysis of safety in animals.

Mutagenicity:

Salmonella/Microsome Test (Ames Assay)

Dinoprostone was tested at doses of 250 - 2000 µg/plate for bacterial mutagenicity in the Salmonella/microsome test using the most sensitive tester strains available (TA98, TA100, TA1537, TA1538 and TA1535). The results showed no evidence of bacterial mutagenicity at any dose with or without an *in vitro* metabolic activation system.

DNA Damage/Alkaline Elution Assay:

Chinese hamster lung fibroblast (V-79) cells were exposed to several dose levels (0.3-3.0 mM) of dinoprostone directly and in the presence of a rat liver metabolizing system. No DNA damage was observed at the several dose levels used. Similar testing of several procarcinogens and carcinogens did produce significant DNA damage. These results suggest that dinoprostone would not likely be carcinogenic in conventional bioassays.

Micronucleus Test

Groups of 5 male rats were administered dinoprostone intraperitoneally at levels of 20, 200, 500 and 2000 µg/kg (1/2 total dose given at 0 and 24 hours). Similar groups of rats received the vehicle or 40 mg/kg cyclophosphamide and served as controls. Thirty hours after the first dose, the rats were sacrificed, the bone marrow harvested and processed for examination and the polychromatophilic erythrocytes examined for micronuclei. Dinoprostone did not significantly increase the incidence of micronucleated polychromatophilic erythrocytes above the control level which the positive control, cyclophosphamide, did. Therefore, under the test conditions employed for this study, dinoprostone did not act as a clastogen or chromosomal mutagen.

Anaphylactic Sensitization Study:

Two lots of dinoprostone were administered via the intracutaneous route to 6 guinea pigs each. Each animal received 10 injections during a 22-day period and a challenge injection of the same material on the 38th day. These lots were judged not to have anaphylactic sensitizing potential.

Reproduction and Teratology:

Perinatal Study in the Rat

Dinoprostone had no observable effect on mortality or weight gain when given to 1 day old rats by subcutaneous injection at 0.1 mg/kg body weight. When administered to pregnant rats on gestation day 20 at the same level, by subcutaneous injection, the compound was judged not to have adverse effects on pups nor were gross pathological lesions noted at necropsy of weanlings.

Modified Teratology Study in the Rat

Pregnant rats were given twice daily subcutaneous injections of 0.25 or 0.5 mg dinoprostone/animal (approximately 1.7 and 3.3 mg/kg/day) on gestation days 9, 10 and 11. The 0.25 mg dose given twice each day produced little effect on maternal weight gain during the remainder of the gestation period and had little effect on litter size or weight. At the 0.5 mg level signs of drug effect included repressed dam weight gain, litter weight and size plus an increase in the number of resorption sites. There were no visceral abnormalities in any of the offspring from treated dams. Skeletal abnormalities were confined to the 0.5 mg group and in some cases were due to teratogenic effect.

Rat Reproduction Study with Proven Breeders

The daily subcutaneous administration of either 1.0 or 3.0 mg/kg dinoprostone to proven breeder female rats for 14 days before breeding resulted in decreased maternal weight gains, fewer pregnancies and slightly smaller litters. There was no drug or dose related increase in the number of pups born dead, and the average weights of pups from treated dams were comparable to those of pups from control rats. All pups from treated rats appeared normal at gross examination.

Teratology Study in the Rabbit

Dinoprostone was given, by subcutaneous injection, to groups of pregnant Belted Dutch rabbits at dosage levels of 0.25 mg/kg b.i.d. and 0.50 mg/kg b.i.d. on days 9, 10 and 11 of gestation. A third group received the vehicle alone, via gastric intubation, from day 6 through day 18 of gestation.

Administration of these dosage levels of dinoprostone did not produce any reproductive, visceral or skeletal defects in the test animals.

A Segment II Teratology Study in the Rabbit

Dinoprostone in absolute ethanol and 0.9 N saline was administered to rabbits subcutaneously on days 9 - 18 of pregnancy at dosage levels of 0, 0.75 and 1.5 mg/kg/day. No evidence of teratogenicity was noted when administered by this route at a dosage level of 1.5 mg/kg or less.

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PART III: CONSUMER INFORMATION**PROSTIN® E₂ Vaginal Gel**
Dinoprostone vaginal gel
Prostaglandin

This leaflet is part III of a three-part "Product Monograph" published when PROSTIN E₂ Vaginal Gel was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PROSTIN E₂ Vaginal Gel. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

PROSTIN E₂ Vaginal Gel is used to induce labour in pregnant women at the end or near the end of pregnancy.

What it does:

PROSTIN E₂ Vaginal Gel is an oxytocic agent, its effect on uterine smooth muscle leads to cervix ripening (opening of the uterus) and results in labour induction.

When it should not be used:

PROSTIN E₂ Vaginal Gel should not be used if:

- You cannot be given Oxytocic drugs or unable to have prolonged contractions of the uterus;
- You have a ruptured amniotic membranes or choriamnionitis (inflammation of the fetal membranes);
- You have unexplained vaginal bleeding during pregnancy
- You are unable to have vaginal delivery;
- You are allergic to prostaglandins or any oxytocic drug or any of the ingredients in **PROSTIN E₂ Vaginal Gel**;
- You have no engagement of the baby's head (baby's head down into the pelvic), or abnormal position of the placenta or umbilical cord; or fetal malpresentation (baby in the difficult position for the birth process);
- You have or have had untreated pelvic inflammatory disease;
- You are having heart, lung, kidney or liver disease.

PROSTIN E₂ Vaginal Gel should not be used together with other oxytocics.

What the medicinal ingredient is:

Dinoprostone

What the important nonmedicinal ingredients are:

Colloidal silicon dioxide and triacetin

What dosage forms it comes in:

PROSTIN E₂ Vaginal Gel is semi-translucent viscous gel in a single dose pre-filled-syringe. Each syringe contains 1.0 mg dinoprostone / 2.0 mL or 2.0 mg dinoprostone/2.5 mL.

Each syringe contains:

1.0 mg dinoprostone (PGE₂)/2.5 mL Syringe (3 gm)
2.0 mg dinoprostone (PGE₂)/2.5 mL Syringe (3 gm)

WARNINGS AND PRECAUTIONS

PROSTIN E₂ Vaginal Gel should be given to you by a doctor experienced in using the drug.

PROSTIN E₂ Vaginal Gel may cause uterine rupture and/or cervical laceration (tearing), and anaphylactoid syndrome of pregnancy (amniotic fluid embolism)

BEFORE you use PROSTIN E₂ Vaginal Gel talk to your doctor if:

- You are 35 years of age and over with complications during pregnancy;
- You have had blood clotting problem after giving birth (post-partum);
- You have or have had seizure;
- You have asthma or glaucoma;
- You have heart, liver, kidney problem.

INTERACTIONS WITH THIS MEDICATION

Before receiving **PROSTIN E₂ Vaginal Gel**, tell your doctor if you are taking other drugs, including non-prescription and natural health products.

PROPER USE OF THIS MEDICATION**Usual dose:**

An initial dose of 1 mg is to be given to you intra vaginally. A dose of 1 mg or 2 mg PROSTIN E₂ Vaginal Gel may be repeated, once, 6 hours later depending upon the response to the initial dose.

You should remain lying down (a lateral or supine position) for 30 minutes after the drug was given to prevent leakage of the gel.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

N/A

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Possible side effects on mother: strong uterine contractions, failed induction, failure to progress, diarrhea, nausea, vomiting, fever, severe allergic reaction (anaphylactic reaction, anaphylactic shock, anaphylactoid reaction), back pain, uterine rupture, abnormal uterine contraction, warm feeling in vagina, cardiac arrest.
- Possible side effects on baby: abnormal heart rate, distress (unwell), still birth.
- Serious side effect reported with the use of **PROSTIN E₂ Vaginal Gel**: blood clots inside the blood vessels throughout the body (disseminated intravascular coagulation).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abnormal labour affecting fetus		✓	
	Fetal distress syndrome		✓	
	Increased uterine contractions		✓	

This is not a complete list of side effects. For any unexpected effects while taking PROSTIN E₂ Vaginal Gel, contact your doctor or pharmacist.

HOW TO STORE IT

Store in a refrigerator at 2-8°C

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.pfizer.ca>

This leaflet was prepared by Pfizer Canada Inc.

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