PRODUCT MONOGRAPH

PREPIDIL®
(dinoprostone gel)

0.5 mg/2.5 ml Syringe (3 gm)

Prostaglandin

Pfizer Canada Inc
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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Distribution : Paladin Labs Inc.
Montréal (Québec)

NAME OF DRUG

PREPIDIL®

(Dinoprostone Gel)

Gel - 0.5 mg / 2.5 ml Syringe (3 gm)

THERAPEUTIC CLASSIFICATION

Prostaglandin

ACTION

PREPIDIL (dinoprostone gel), which contains a prostaglandin E_2 analogue as the active ingredient, causes cervical ripening preparatory to the onset of labour when it is administered endocervically. Although the local effects of prostaglandin E_2 on cervical maturation is not specifically known, experimental data indicates the drug enhances cervical hemodynamics which in turn promotes ripening of the cervix.

INDICATIONS AND CLINICAL USES

PREPIDIL (dinoprostone gel), administered into the cervical canal, is indicated for inducing cervical softening and dilatation of the cervix in pregnant women at or near term, where cervical features are not conducive to induction.

The use of PREPIDIL in this manner, in patients with unfavourable induction features prior to labour induction by conventional methods, has been shown to improve the overall outcome of labour induction attempt.

CONTRAINDICATIONS

Endocervically administered PREPIDIL (dinoprostone gel) is not recommended for use in the following:

l. 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 a major degree of 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, polyhydromnias).
2. Patients with ruptured amniotic membranes or suspected chorioamnionitis;
3. Patients with known hypersensitivity to the prostaglandins or any ingredient in the formulation;
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.

PREPIDIL should not be used simultaneously with other oxytocics (see WARNINGS).

PREPIDIL should not be used in patients with a history of epilepsy.

WARNINGS

PREPIDIL (dinoprostone gel), 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 use of oxytocin following pre-induction cervical ripening with PREPIDIL has been studied. Prostaglandins may potentiate the effect of oxytocin on the uterus. Therefore, to preclude inappropriate augmentation of one oxytocic agent with another, it is recommended that induction with an oxytocic agent not be implemented until six (6) to twelve (12) hours after application of PREPIDIL for cervical ripening. Patients requiring oxytocin induction after PREPIDIL administration should be carefully monitored.

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 PREPIDIL (dinoprostone gel), uterine activity, fetal status and the character of the cervix (dilatation and effacement) should be carefully monitored to detect possible evidence of undesired responses. These include hypertonus, sustained uterine contractility or fetal distress. In cases where there is a known history of hypertonic uterine

contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the fetus should be continuously monitored. The possibility of uterine rupture and/or cervical laceration should be born in mind where high-tone myometrial contractions are sustained.

Cephalopelvic relationships should be carefully evaluated before the use of PREPIDIL.

Caution should be exercised in the administration of PREPIDIL in patients with the following medical conditions:

Asthma or a history of asthma;
Glaucoma or raised intraocular pressure.

Prostaglandins are excreted in breast milk at very low concentrations. No measurable differences were observed in the milk of mothers delivering prematurely and at term.

Prolonged treatment of newborn infants with prostaglandin E_1 can induce proliferation of bone. There is no evidence that short term administration of prostaglandin E_2 can cause similar bone effects.

Caution should be taken not to administer PREPIDIL above the level of the internal os. Placement of PREPIDIL into the extra-amniotic space has been associated with uterine hyperstimulation.

Patients with severe renal disease and/or severe hepatic disease accompanied by metabolic aberrations should be dosed with caution.

Drug Interactions

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

ADVERSE REACTIONS

In clinical trials of PREPIDIL (dinoprostone gel), the most commonly seen reactions were intrapartum fetal heart rate changes and unclassified fetal distress during or subsequent to PREPIDIL administration. The adverse reaction incidences reported below are from the clinical trials (0.5 mg administered endocervically) in which oxytocin was used as the control. The control group had comparable incidences of adverse events.

Fetal Effects (l6%):

Intrapartum fetal heart rate changes including bradycardia and unclassified fetal distress during or subsequent to Prepidil Gel treatment (l3%);

Uterine contractile abnormalities with fetal heart rate changes (3%);

Depressed neonates at birth (Apgar Scores below 7):

l minute (l3%)

5 minutes (l%)

Maternal Effects (l0%):

Uterine contractile abnormalities without fetal heart rate changes (5%);

Gastrointestinal effects (vomiting and/or diarrhea - 5%)

Miscellaneous (≥1%)

- Fever
- Back pain
- Warm feeling in vagina

Post-Marketing Adverse Drug Reactions

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labor was induced by pharmacological means, either with dinoprostone or oxytocin (see section **WARNINGS**). The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labors).

Adverse event reports not listed above that have been received from spontaneous post-marketing reports for PREPIDIL since market introduction are shown below.

Immune system disorders: Hypersensitivity reactions (e.g. Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction)
Gastrointestinal disorders: Nausea
Pregnancy, puerperium and perinatal conditions: Uterine rupture

OVERDOSE\

Overdosage with PREPIDIL 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

The recommended dose of PREPIDIL (dinoprostone gel) is 0.5 mg. Each prefilled syringe contains
3 grams (2.5 mL) of gel which, in turn contains 0.5 mg dinoprostone.

This product is intended for single dose administration.

Utilizing the catheter provided, administer the entire contents of the syringe by gentle expulsion into the cervical canal just below the level of the internal cervical os. No attempt should be

made to administer the small amount of gel remaining in the catheter. Care should be taken not to administer PREPIDIL above the level of the internal os. Placement of the gel into the amniotic space has been associated with uterine hyperstimulation. (See PRECAUTIONS)

After placement of the gel, the patient should be instructed to remain in the dorsal position for l0 - l5 minutes to minimize gel leakage.

DOSAGE FORMS

Availability

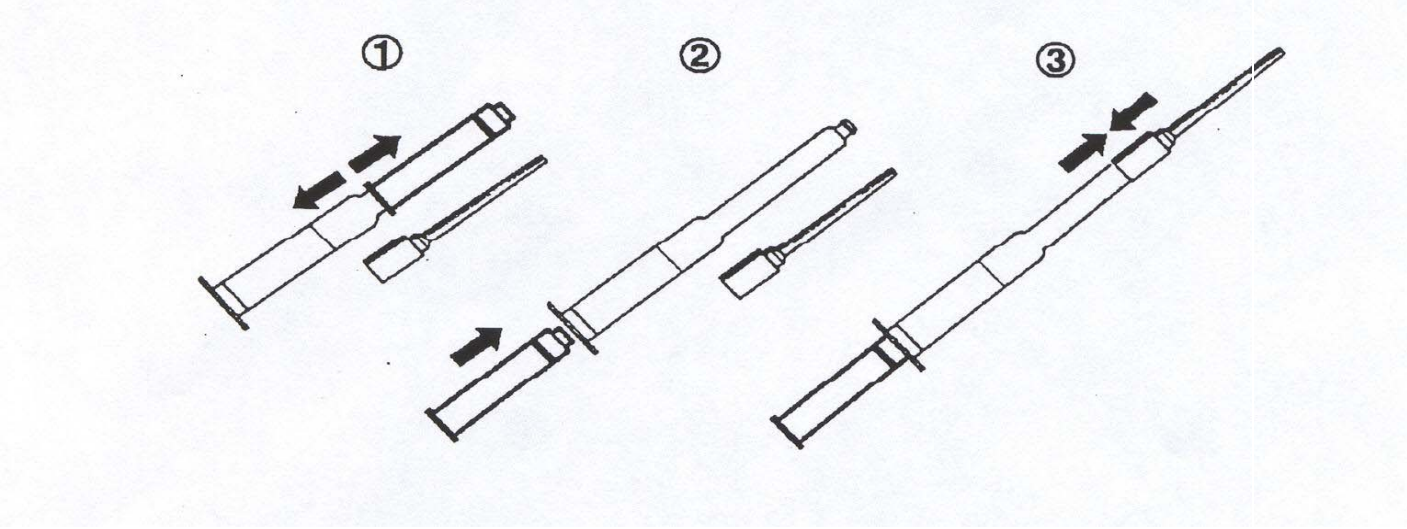
PREPIDIL (dinoprostone gel) is supplied as a translucent sterile gel preparation in a prefilled syringe with an accompanying catheter. Each syringe contains:

Medicinal ingredients: dinoprostone (PGE_2) 0.5 mg, syringes of 3.0 g (2.5 mL)
Non medicinal ingredients: colloidal silicon dioxide and triacetin

SEE DIAGRAM FOR ASSEMBLY INSTRUCTIONS (APPENDIX A)

APPENDIX A

Syringe Assembly Instructions



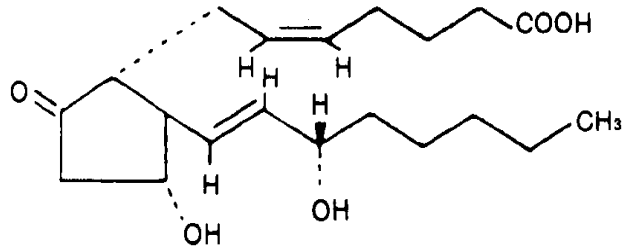
1. Remove protective end cap (to serve as plunger rod).
2. Insert protective end cap into the syringe.
3. Firmly attach catheter hub to syringe tip (catheter has to click into place) and administer syringe content.

PREPIDIL has a shelf life of 24 months when stored at 4°C, under continuous refrigeration.

PHARMACEUTICAL INFORMATION

Structural Formula and Chemistry

Dinoprostone



Molecular Formula: $C_{20}H_{32}O_5$

Molecular Weight: 352.5

Chemical Name: (5z,ll-alpha,l3E,l5S)-ll,l5-Dihydroxy-9-oxo-prosta-5,l3-dien-l-oic acid.

Description: PREPIDIL - 0.5 mg is a translucent, thixotropic gel formulation containing 0.5 mg dinoprostone as the active ingredient in each unit dose of 3.0 grams (2.5 mL). Dinoprostone is a white crystalline powder. It has a melting point range of 64°C to 7l°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/l00 mL.

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, l0 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 non-toxic to the nonpregnant mice. It caused fetal death in the pregnant mice.

Dinoprostone was injected subcutaneously into rats (2mg/rat/day) on days 4, 5 and 6 of pregnancy. Only 1 out of 6 animals was pregnant on day 10. Dinoprostone injected subcutaneously (l 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 l0 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 l5 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 x 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 vasodilation. 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 μg or as a continuous intravenous infusion of 8 μg/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 l0 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 l7, l8-$^{3}H_2$ dinoprostone, 5% of the radioactivity remained in the blood, decreasing to l.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:

l. 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.l% 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.l% of the dose remains in any of the tissues measured except for the lower small intestine and large intestine.

CLINICAL PHARMACOLOGY

PREPIDIL (dinoprostone gel) - 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 PGE_2 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 PGE_2 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 PGE_2 gel treated patients compared to 3.1% for controls; (2) an incidence of intrapartum fetal heart rate changes during or subsequent to PGE_2 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 PGE_2 gel for preinduction cervical softening.

In both laboratory animals and man, large doses of PGE_2 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. PGE_2 is also capable of stimulating the smooth muscle of the gastrointestinal tract. This property may be responsible for the vomiting and/or diarrhea that are sometimes associated with the use of PGE_2.

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-13-11B-16-cyclo PGE_2, 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. PGE_2 is 73% bound to human plasma albumin as determined by equilibrium dialysis.

PGE_2 is rapidly metabolized in the lungs, kidneys, spleen and liver. A single pass of an injected PGE_2 dose in the circulatory system converts 90% of PGE_2 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 PGE_2, 50% of the injected radioactivity was recovered in the urine in two hours and 67% was recovered in 12 hours.

TOXICOLOGY

Acute Toxicity:

The LD_{50} values for single dose dinoprostone administration are summarized below:

SPECIES	ROUTE	LD_{50} (mg/kg)	OTHER
Mouse	Intravenous	158	-
Mouse	Oral	500	-
Rat	Intravenous	45	-
Rat	Oral	513	-
Mouse	Intravenous	-	Not Toxic at 30mg/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 mcg/kg/min. for 2 hours daily intravenously for 5 days, 5 mg/kg/day orally for 5 days and up to l8 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 mcg/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 (l/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

PREPIDIL Gel
dinoprostone gel

This leaflet is part III of a three-part "Product Monograph" published when PREPIDIL 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 PREPIDIL Gel. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PREPIDIL gel is used to start the "cervical softening" and dilation of the cervix in pregnant women at the end of pregnancy.

What it does:
PREPIDIL gel is an oxytocic agent, its effect on uterine smooth muscle leads to the cervix ripening (opening of the uterus) and results in labour induction.

When it should not be used:
PREPIDIL gel should not be used if:

- You cannot be given Oxytocic drugs or unable to have prolonged contractions of the uterus;
- You have ruptured amniotic membranes or choriamnionitis (inflammation of the fetal membranes)
- You have unexplained vaginal bleeding during pregnancy;
- You are unable to have vaginal delivery;
- When drugs used to stimulate labour are not required or when prolonged contraction of the uterus may be harmful to the baby's safety or stability of the uterus
- You are allergic to prostaglandins or any other oxytocic drug or any of the other ingredients in PREPIDIL Gel;
- You have no engagement of the baby head (baby's head down into the pelvis), 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; PREPIDIL gel should not be used together with other oxytocics.

What the medicinal ingredient is:
Dinoprostone (PGE_2)

What the important nonmedicinal ingredients are:
Colloidal silicon, dioxide and triacetin

What dosage forms it comes in:
PREPIDIL is supplied as a translucent sterile gel preparation in a prefilled syringe with an accompanying catheter.

Each syringe contains:
0.5 mg dinoprostone (PGE_2)/2.5 mL Syringe (3 g)

WARNINGS AND PRECAUTIONS

PREPIDIL should be given to you by doctor experienced in using this drug.

PREPIDIL gel may cause uterine rupture and/or cervical laceration (tearing), and anaphylactoid syndrome of Pregnancy (amniotic fluid embolism).

BEFORE you use PREPIDIL 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 PREPIDIL gel, tell your doctor if you are taking other drugs, including non-prescription and natural health products.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose of PREPIDIL (dinoprostone gel) is 0.5 mg equivalent to the use of one prefilled syringe. Each syringe is intended for single dose administration.

After you doctor has placed the gel, you should remain lying on your back for 10-15 minutes to minimize gel leakage.

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 (10%), including uterine contractile abnormalities without fetal heart change (5%),

vomiting and diarrhea (5%), fever (>1%), back pain (>1%), warm feeling in vagina (>1%).

Possible side effects on baby (16%), including fetal heart rate change and unclassified fetal distress (13%), uterine contractile abnormalities with fetal heart change (3%), and depressed neonates (13 % at 1 minute):

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		✓	
	Uterine hypertonus		✓	
Uncommon	Nausea, vomiting, diarrhea		✓	✓

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

HOW TO STORE IT

Store in a refrigerator at a temperature lower than 4°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
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