

PRODUCT MONOGRAPH

PROSTIN® E₂ TABLETS

dinoprostone

0.5mg

Prostaglandin

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ACTION AND CLINICAL PHARMACOLOGY

Orally administered 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 labor. Whether or not this action results from a direct or indirect effect of dinoprostone on the myometrium has not been determined with certainty.

Dinoprostone is also capable of stimulating the smooth muscle of the gastrointestinal tract of man. This property may be responsible for the nausea-vomiting and/or diarrhea that is sometimes associated with the use of dinoprostone.

INDICATIONS AND CLINICAL USE

PROSTIN E₂ (dinoprostone) is indicated as a uterine stimulant for induction of labor at or near term in:

1. Elective induction.
2. Indicated induction such as: postmaturity, hypertension, toxemia of pregnancy, premature rupture of amniotic membranes, Rh incompatibility, diabetes mellitus, intra-uterine death, or fetal growth retardation.

CONTRAINDICATIONS

PROSTIN E2 (dinoprostone) should not be used in patients with known hypersensitivity to dinoprostone or any other constituents of the tablet (corn starch, colloidal silicon dioxide, lactose anhydrous, magnesium stearate powder; food grade, microcrystalline cellulose).

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. Engagement of the head has not taken place;
3. Patients with unexplained vaginal bleeding during this pregnancy;
4. Patients with fetal malpresentation;
5. Patients with gynecological, obstetrical or medical conditions that preclude vaginal delivery.
6. Patients whose pregnancy is complicated by an abnormal position of the placenta or umbilical cord.

7. Patients with a past history of, or existing pelvic inflammatory disease, unless adequate prior treatment has been instituted;
8. Patients with active cardiac, pulmonary, renal or hepatic disease.

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

WARNINGS

PROSTIN E₂ (dinoprostone), like other effective oxytocic agents, should be used with strict adherence to recommended dosages, by medically trained personnel in hospital surroundings that can provide immediate intensive care and facilities for immediate surgical intervention.

The sequential use of oxytocin immediately following PROSTIN E₂ has been carried out. It has been found that prostaglandins might potentiate the effect of oxytocin. THEREFORE, INFUSION OF OXYTOCIN SHOULD NOT BE STARTED UNTIL AT LEAST ONE HOUR HAS ELAPSED FOLLOWING THE LAST ORAL DOSE OF PROSTIN E₂.

Reports of epileptic seizures with other forms of prostaglandin by routes other than oral 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 Tablets 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 tablets (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 tablets, 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 tablets.

PROSTIN E2 tablets 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.

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.

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 tablets, 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

The most frequent adverse reactions observed with the use of PROSTIN E₂ (dinoprostone) for the induction of labor are vomiting, with or without nausea and diarrhea. These side effects occur in about 21% of patients induced with a total dose of 0.5 - 3.0 mg (1 - 6 tablets) of PROSTIN E₂, in about 39% of patients induced with a total dose of 3.5 - 6.0 mg (7 - 12 tablets) of PROSTIN E₂ and in about 50% of patients induced with a total dose of more than 6.0 mg (more than 12 tablets) of PROSTIN E₂.

Fetal heart rate changes were observed in 6.5% of patients induced with PROSTIN E₂.

Uterine hypertonus occurred in 3.1% of patients. It is usually manageable by the temporary discontinuation of PROSTIN E₂, a reduction in the dose of PROSTIN E₂, and the administration of oxygen. In the rare instance where these measures are not effective, prompt delivery is indicated.

Other side effects reported in less than 1% of patients include the following: headache, hypertension, hypotension, postpartum hemorrhage, fever, dizziness, chills, hiccough, flushing, tachycardia, dyspnea, bronchospasm, rash. The relationship of these side effects to PROSTIN E₂ therapy has not been established.

Maternal Adverse Events. The following maternal adverse events have been reported with use of the oral tablets:

Cardiac disorders: Cardiac arrest

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

Nervous system disorders: Transient vasovagal symptoms (flushing, shivering, headache, dizziness)

Pregnancy, puerperium and perinatal conditions: Uterine contractile abnormalities (increase frequency, tone, or duration), abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation, uterine rupture

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Skin and subcutaneous tissue disorders: Rash

Vascular disorders: Hypertension

Fetal Adverse Events. The following fetal adverse events have been reported with use of the oral tablets:

Investigations: Fetal distress / altered FHR including bradycardia, neonatal distress / low Apgar score

Pregnancy, puerperium and perinatal conditions: Neonatal death, still birth

Post-Marketing Adverse Drug Reaction:

Blood and lymphatic system disorders: Disseminated intravascular coagulation

OVERDOSE

Overdosage with PROSTIN E₂ TABLETS 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.

Hyperpyrexia may occur. Patients who are pregnant should be carefully observed for severe uterine hypercontractility and uterine hypertonus. Because of the extremely short duration of action of PROSTIN E₂ once it is absorbed, no specific treatment to counteract drug effect need be taken. However, vomiting should be induced (if not already occurring) to remove any unabsorbed drug from the stomach.

In one published report, the intravenous infusion of 500 mL of 10 per cent ethanol per hour for one hour inhibited uterine activity initiated and maintained by an infusion of either prostaglandin F₂ α or E₂ when given simultaneously with the prostaglandin.

DOSAGE AND ADMINISTRATION

An initial dose of 0.5 mg (one tablet) should be given followed in one hour by a second dose of 0.5 mg (one tablet). All subsequent doses should be given hourly. The lowest dosage that will produce satisfactory uterine response should be used. All doses should be taken with a small amount of water.

For patients with a parity of 2 or greater, and those with a Bishop Score of 6 or greater (see Table below), it is recommended that 0.5 mg of PROSTIN E₂ (dinoprostone) be administered hourly and maintained throughout the induction (unless excessive uterine activity dictates elimination of the hourly dose). In nulliparous or multiparous patients who are historically resistant to induction (Bishop Score of 0 - 5), an increment in individual doses may be justified. If satisfactory labor has not been initiated in these patients after two (2) hours of administration of PROSTIN E₂, subsequent doses may be increased by 0.5 mg (one tablet) increments at each hourly interval. A SINGLE DOSE SHOULD NEVER EXCEED 1.5 mg (3 tablets).

Once labor has been initiated (regardless of the dose), it is recommended that 0.5 mg (one tablet) of PROSTIN E₂ be given hourly for maintenance of the progress of labor. It may, however,

prove reasonable to occasionally eliminate this maintenance dose to determine if labor will progress without additional medication.

If vomiting occurs at any time during the treatment period, examine the vomitus for the presence of an intact tablet of PROSTIN E₂. If one is found, the dose should be repeated at once. If only a part or parts of the tablet is (are) seen (this is considered as evidence of tablet disintegration) or, if no tablet is seen in the vomitus, the dose should not be repeated and the next dose should be given only at the scheduled time. If two (2) successive doses are vomited and an intact tablet is seen each time, it is recommended that the patient be allowed to rest until the next scheduled dose. The effectiveness of medication to treat the nausea and/or vomiting which may occur with the use of PROSTIN E₂ has not been determined.

Uterine activity is considered excessive if the frequency of contractions is greater than 5 per 10 minutes and/or the internal tonus consistently exceeds 15 mm Hg. In this event, administration of PROSTIN E₂ should be stopped to allow stabilization and evaluation. Note: The intravenous administration of 10% ethyl alcohol may reverse the effect of PROSTIN E₂.

If PROSTIN E₂ fails to elicit regular uterine contraction by the end of 8 hours, the case should be classified as a failed induction. Subsequent management is left to the discretion of the physician.

**THE TOTAL TREATMENT PERIOD WITH PROSTIN E₂ SHOULD NOT, IN ANY
INSTANCE, EXCEED 18 HOURS.**

| PELVIC SCORE | | | | |
|--------------|--------|---------|---------|-------|
| cm | 0 | 1 – 2 | 3 - 4 | 5 - 6 |
| Dilatation | 0 | 1 | 2 | 3 |
| % | 0 - 30 | 40 - 50 | 60 - 70 | 80 |
| Effacement | 0 | 1 | 2 | 3 |
| | -3 | -2 | -1 0 | +1 +2 |
| Station | 0 | 1 | 2 | 3 |
| | Firm | Med. | Soft | |
| Consistency | 0 | 1 | 2 | |
| | Post. | Mid. | Ant. | |
| Position | 0 | 1 | 2 | |

Bishop Method of Pelvic Scoring

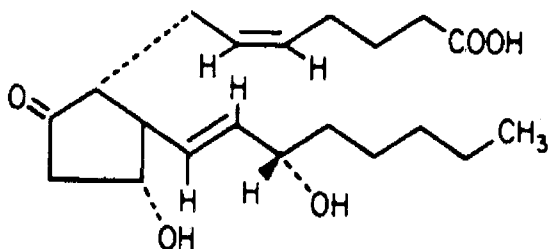
PHARMACEUTICAL INFORMATION

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:



Empirical Formula: C₂₀H₃₂O₅

Molecular Weight: 352.46

Description:

PROSTIN E₂ (dinoprostone) occurs as a white to off-white crystalline powder. It has a melting point within the range of 64°C to 71°C. It is soluble in ethanol and in 25% ethanol in water. It is soluble in water to the extent of 1.00 - 1.05 mg/mL at 25°C.

Stability and Storage Recommendation:

PROSTIN E₂ tablets should always be stored under normal refrigeration (2-8°C), and they are stable for at least 2 years under these conditions. Once the bottle is opened, the tablets should be used within 90 days.

AVAILABILITY

PROSTIN E₂ (dinoprostone) is supplied in glass bottles containing 10 tablets each. Each white, rectangular compressed tablet has one surface embossed to resemble the letter “U” on one side, and “76” on the other side. Each tablet contains:

Medicinal ingredient: dinoprostone (PGE₂) 0.5 mg per tablet

Non medicinal ingredients: corn starch, colloidal silicon dioxide, lactose anhydrous, magnesium stearate powder; food grade, microcrystalline cellulose.

PHARMACOLOGY

Studies related to primary therapeutic activity:

Pregnancy was interrupted in hamsters, rats and Rhesus monkeys by administering dinoprostone (PROSTIN E₂). In addition, 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 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 day 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.

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.

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 effect 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 as modulators. Studies have shown that the phosphodiesterase activity in mouse brain synaptic vesicles was inhibited by 58% at dinoprostone concentration of $1 \times 10^{-3}M$. 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 $\mu g/min$. 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.

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 was 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 labeled 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 radio-actively labeled dinoprostone have been conducted in female rats following intravenous, oral, intrauterine, and intra-vaginal 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 labeled 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-Hydroxy prostaglandin dehydrogenase 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 varied 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 labeled 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.

Human Studies:

Intravenously administered dinoprostone is extremely rapidly distributed and metabolized in man. Within 1.5 minutes only about 3% of the administered dose remains in the blood as unchanged drug, whereas over 40% of the dose is present as the metabolite, 11 α -hydroxy-9,15-dioxoprost-5-enoic acid. At least nine metabolites of dinoprostone have been identified in human blood and urine. Studies with these metabolites in the rat blood pressure assay and smooth muscle assays indicate a much lower level of activity than the parent compound. In the amount present from a therapeutic dose of dinoprostone in humans, there is felt to be essentially no activity. Dinoprostone is cleared from the blood with a half-life of less than 1 minute and the metabolites with a half-life of less than 10 minutes.

TOXICOLOGY

Acute Toxicity:

| <u>Species</u> | <u>Route</u> | <u>LD₅₀ (mg/kg)</u> |
|----------------|--------------|--------------------------------|
| Mouse | Intravenous | 158 |
| Rat | Intravenous | 45 |
| Rat | Oral | 513 |

Subacute Toxicity:

Five Day Oral Toxicity Study in the Rat:

Dinoprostone was given to groups of 10 female rats orally in single daily doses of 1 and 5 mg/kg/day for 5 days. A similar group of rats received the vehicle alone and served as controls. Dinoprostone was considered non-toxic in this study.

Five Day Oral Toxicity in the Dog:

Dinoprostone was given to groups of four female dogs at oral dose levels of 1 and 5 mg/kg/day for 5 days. A similar group of dogs received empty gelatin capsules and served as controls. The material was considered pharmacologically active and non-toxic.

Chronic Toxicity:

Dinoprostone has been administered intravenously in the dog for 10 days (0.03 mg/kg/day), intravenously in the monkey and rat for 14 days (1.5 mg/kg/day), and topically in the rat for 21 days (10 mg/ml). Dinoprostone was considered to be non-toxic in these studies.

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 effect 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.

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.

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PART III: CONSUMER INFORMATION

PROSTIN® E₂ Tablets Dinoprostone Prostaglandin

This leaflet is part III of a three-part "Product Monograph" published when PROSTIN® E₂ Tablets 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 Tablets. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

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

What it does:

PROSTIN® E₂ Tablets 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:

PROSTIN® E₂ Tablets should not be used if:

- You cannot be given Oxytocic drugs or unable to have prolonged contractions of the uterus;
- 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 of the other ingredients in the PROSTINE E₂ tablets;
- You have no engagement of the baby 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 Tablet should not be used together with other oxytocics

What the medicinal ingredient is:

Dinoprostone

What the important nonmedicinal ingredients are:

Corn starch, colloidal silicon dioxide, lactose anhydrous, magnesium stearate powder; food grade, microcrystalline cellulose.

What dosage forms it comes in:

PROSTIN® E₂ Tablets are in glass bottles containing 10 tablets each.

WARNINGS AND PRECAUTIONS

PROSTIN® E₂ Tablets should be given to you only by doctor experienced in using the drug.

BEFORE you use PROSTIN® E₂ Tablets talk to your doctor if:

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

INTERACTIONS WITH THIS MEDICATION

Before receiving PROSTIN E₂ Tablets, tell your doctor if you are taking others drugs including non-prescription and natural health products.

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dose of PROSTIN® E₂ Tablets is 0.5 mg (one tablet) followed in one hour by a second dose of 0.5 mg (one tablet). All subsequent doses should be given hourly. The lowest effective dose should be used. All doses should be taken with a small amount of water.

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

In studies the most commonly reported adverse reactions were vomiting, with or without nausea and diarrhea (21% at dose 0.5 – 3.0 mg).

Other adverse reactions include Fetal heart changes (6.5%), uterine hypertonus (3.1%), and fetal distress syndrome.

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

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 | | √ | |
| | Uerine hypertonus | | √ | |
| Uncommon | Nausea, vomiting, diarrhea | | √ | √ |

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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This is not a complete list of side effects. For any unexpected effects while taking PROSTIN® E₂ Tablets, 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