PRODUCT MONOGRAPH

^{Pr}PROSTIN® $F_{2\alpha}$

(Dinoprost Tromethamine, USP)

Sterile solution for injection
5 mg/mL

PROSTAGLANDIN

Pfizer Canada Inc.
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PART I: HEALTH PROFESSIONAL INFORMATION

WARNING: For Intra-amniotic Injection Only

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Inter-amniotic	Sterile solution for injection, 5 mg/mL	Benzyl alcohol, hydrochloric acid, sodium hydroxide, water for injection. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

PROSTIN $F_{2\alpha}$ (dinoprost) is indicated for the termination of pregnancy in the second trimester between 12th to 18th week of gestation by the intra-amniotic administration of the drug.

Note: This drug is sold as an abortifacient for use only in circumstances not prohibited by the Criminal Code of Canada.

CONTRAINDICATIONS

PROSTIN $F_{2\alpha}$ (dinoprost) is contraindicated in patients known to be hypersensitive to this drug or any of its related analogues. PROSTIN $F_{2\alpha}$ is also contraindicated in the presence of acute pelvic inflammatory disease and patients with active cardiac, pulmonary, renal or hepatic disease.

WARNINGS AND PRECAUTIONS

General

PROSTIN $F_{2\alpha}$ (dinoprost) is for intra-amniotic administration only. The myometrial contractions induced by intra-amniotic administration of PROSTIN $F_{2\alpha}$ are sufficient to produce evacuation of the products of conception from the uterus in the majority of cases. PROSTIN $F_{2\alpha}$ does not appear to directly affect the fetal placental unit. For this reason the potential viability of the fetus must be considered before PROSTIN $F_{2\alpha}$ is administered.

Concomitant use with other oxytocic agents is not recommended (see DRUG INTERACTIONS – Drug-Drug Interactions).

PROSTIN $F_{2\alpha}$ and hypertonic saline should not be used concurrently for the termination of a pregnancy (see DRUG INTERACTIONS – Drug-Drug Interactions).

It is not advisable to use hypertonic saline subsequent to PROSTIN $F_{2\alpha}$ while PROSTIN $F_{2\alpha}$ induced uterine activity is still present (see DRUG INTERACTIONS – Drug-Drug Interactions).

A few primigravida patients have experienced cervical perforation during abortion induced by intra-amniotic administration of PROSTIN $F_{2\alpha}$ (dinoprost) when intravenous oxytocin has been used concomitantly stimulating uterine hypertonus in the presence of an undilated or poorly dilated cervix. It is recommended that concomitant intra-amniotic administration of PROSTIN $F_{2\alpha}$ and intravenous oxytocin be used with caution in the absence of adequate cervical dilatation. As cervical trauma can occur without remarkable symptomatology, it is further recommended that each patient be carefully examined post-abortion to exclude such possibilities.

As in spontaneous abortion, where the process is sometimes incomplete PROSTIN $F_{2\alpha}$ induced abortion may sometimes be incomplete. In such cases, other measures should be taken to assure complete abortion.

Carcinogenesis and Mutagenesis

Evidence from some animal studies has suggested that certain prostaglandins may have some teratogenic potential. Therefore any failed pregnancy termination with PROSTIN $F_{2\alpha}$ must be completed by some other means.

Cardiovascular

In patients with a history of hypertension or cardiovascular disease, PROSTIN $F_{2\alpha}$ should be used with caution.

Neurologic
In patients with past history of epilepsy, PROSTIN F2α should be used with caution.

Literature reports of epileptic seizures in association with intra-amniotic administration of PROSTIN $F_{2\alpha}$ have been published. The association of PROSTIN $F_{2\alpha}$ with seizures has not been conclusively proven. However, it is recommended that PROSTIN $F_{2\alpha}$ be used in known epileptics only when the epilepsy is under good control and then only with maximum care and observation on the part of the physician in charge.

Ophthalmologic
In patients with a history of glaucoma, PROSTIN F2α should be used with caution.

Respiratory
In patients with a history of asthma, PROSTIN F2α should be used with caution.

Sexual Function/Reproduction
As with any oxytocic agent, PROSTIN $F_{2\alpha}$ should be used with caution in patients with compromised (scarred) uteri.

Special Populations

Pregnant Women: Any failed pregnancy termination with PROSTIN $F_{2\alpha}$ must be completed by some other means as certain prostaglandins may have some teratogenic potential.

PROSTIN $F_{2\alpha}$ contains benzyl alcohol which can cross the placenta. Adverse outcomes associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration are not known.

Pediatrics: The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Premature and low-birth weight infants may be more likely to develop toxicity. Benzyl alcohol may be harmful to the unborn child.

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 E_1 during prolonged treatment. There is no evidence that short term administration of PROSTIN $F_{2\alpha}$ can cause similar bone effects.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The most frequent adverse reactions observed with the use of PROSTIN $F_{2\alpha}$ (dinoprost) for abortion are related to its contractile effect on smooth muscle. When administered intra-amniotically to 777 patients in varying dosages, vomiting was experienced by 57.1% of patients, nausea by 24.8% of patients and diarrhea by 16.1% of patients.

Initial blood loss prior to abortion occurred in 362 cases (48.9%). Only 27 (3.6%) experienced total blood loss (before, during and after abortion) of greater than 500 mL and only six (0.8%) experienced blood loss of greater than 1000 mL. Nine patients (1.2%) required blood replacement.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

All other side effects that were reported occurred in less than 1.0% of patients. The only other complaint noted was that of abdominal or uterine pain, which is to be expected during the course of an induced abortion.

Rupture of the upper intervaginal cervix posteriorly into the vagina was reported in five patients (0.6%). In all five cases the status of the cervix was described as undialated or poorly dilated prior to the expulsion of the fetus or shortly before rupture of the posterior upper cervix. In four out of the five cases, additional oxytocic intravenous uterine stimulation was used as well as the intra-amniotic administration of PROSTIN $F_{2\alpha}$. Two cases of ruptured uterus were reported, one due to a rupture of a right cornual pregnancy (interstitial) and the other following repeated attempts to remove a placenta in the presence of a constriction ring. This latter case has concomitant use of intra-amniotic PROSTIN $F_{2\alpha}$ and hypertonic saline.

Eight patients were reported to have had convulsions in 1850 patients treated for an incidence of 0.43%. Three were known epileptics under therapy and two of these had seizures following the termination of PROSTIN $F_{2\alpha}$ therapy.

The third had a petit mal seizure prior to the abortion of the fetus 4 hours and 15 minutes after the administration of PROSTIN $F_{2\alpha}$. Two of these three had additional fluid given intravenously and it is more likely that excessive fluid retention and "water-loading", especially in pregnant patients, may have been etiological factors. One patient had a convulsive seizure that occurred after the administration of lidocaine for the introduction of the intra-amniotic catheter but before the administration of PROSTIN $F_{2\alpha}$. One patient had an episode of hyperflexion 10 hours after

the administration of 30mg of PROSTIN $F_{2\alpha}$ but gave a history of similar episodes in previous pregnancies. This case may or may not be related to PROSTIN $F_{2\alpha}$ therapy.

Two other patients had significant amounts of bleeding associated with the abortion and it is felt that hypotension may have contributed to these seizures. In Canadian clinical trials involving 250 patients, five known epileptics were treated with PROSTIN $F_{2\alpha}$ and none had any convulsive attacks. One of these five was an uncontrolled epileptic.

Two patients had severe systemic reactions suggestive of accidental rapid systemic (intra-arterial or intravenous) administration of PROSTIN $F_{2\alpha}$. In one case, the patient had a violent vomiting episode, followed by transient dyspnea, wheezing respiration associated with bronchospasm and rales in both lung fields, tachycardia and hypertension. The patient recovered very quickly without therapy and blood pressure, pulse and respirations returned to their initial levels. The second patient, one minute after an initial dose of 25 mg of dinoprost, developed severe nausea, vomiting and diarrhea. Her blood pressure rose from 110/60 to 150/110 and quickly returned to normal. The patient tolerated a further 25 mg of dinoprost without further reaction.

There were five cases of intra-uterine infection for an incidence of 0.6%. It may be reasonably considered that intra-uterine infection in these cases was a concurrent event of therapeutic termination of mid-trimester pregnancy especially since the majority of cases (four out of five) were associated with retained placenta or a prior dead fetus.

Other adverse reactions in decreasing order of their frequency observed with the use of PROSTIN $F_{2\alpha}$ for abortion but not clearly drug related include:

Cardiac disorders: Chest constriction, heart block (2^{nd} degree)

Eye disorders: Diplopia

General disorders: Malaise, polydipsia

Metabolic disorders: Hematuria

Musculoskeletal and connective tissue disorders: Backache

Nervous system disorders: Drowsiness, vasomotor symptoms, vaso-vagal symptoms, chills, diaphoresis, dizziness, flushing, hot flash, headache, pain – other than uterine (unspecified, epigastric, substernal chest, leg, shoulder), parathesia (unspecified and leg), burning sensation in breast and in eye

Psychiatric disorders: Anxiety

Respiratory, thoracic and mediastinal disorders: Coughing, hiccough, hyperventilation

Reproductive system and breast disorders: Breast tenderness

Urinary disorders: Dysuria, hematuria, urine retention

Abnormal Hematologic and Clinical Chemistry Findings

During clinical trials many clinical laboratory procedures were performed before and immediately after dinoprost therapy and also 12 hours after discontinuation of therapy. There was no clinically significant change in hematocrit or hemoglobin, but there was a consistent tendency toward leucocytosis. Platelets remained unchanged. Total and direct bilirubin remained unaltered, as did serum creatinine, alkaline phosphatase and S.G.O.T. High initial 17-hydroxy-corticosteroids values were noted, which fell to normal levels 12 hours after therapy. These initial high levels were thought to be due to the stress and anxiety associated with pregnancy termination. There was a tendency for an increase in blood glucose to occur during therapy, but it must be noted that these levels were not fasting levels and in some cases were associated with oral ingestion of sugar or intravenous infusion of glucose solutions. Serum electrolytes (serum potassium, serum sodium and serum chloride) showed no significant alteration.

DRUG INTERACTIONS

Drug-Drug Interactions

Concomitant use with other oxytocic agents is not recommended.

It is not advisable to use hypertonic saline subsequent to PROSTIN F2α (dinoprost) while PROSTIN F2α induced uterine activity is still present.

PROSTIN F2α and hypertonic saline should not be used concurrently for the termination of a pregnancy.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

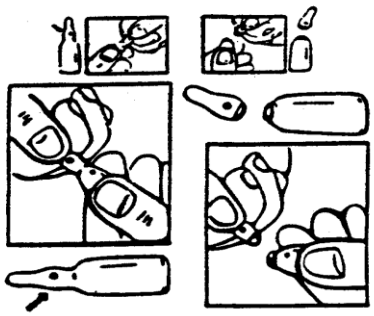
A transabdominal tap of the amniotic sac should be accomplished with an appropriately-sized needle and at least one ml of amniotic fluid should be withdrawn to confirm the presence of the needle in the amniotic sac.

DO NOT INJECT MEDICATION IN THE PRESENCE OF A BLOODY TAP.

Forty milligrams (8 ml) of PROSTIN $F_{2\alpha}$ should then be injected slowly intra-amniotically. It is recommended that the first 1 mL be injected very slowly to determine possible sensitivity prior to completing the total 40 mg dose. This precautionary injection of 1 mL initially also allows observation of the patient for any sign indicative that the medication is being administered intravascularly (which may occur even in the absence of a blood tap).

If within 24 hours of the initial dose, the abortion process has not been established or complete and the membranes are still intact, an additional 10 to 40 mg (2-8 mL) of PROSTIN $F_{2\alpha}$ may be administered by a second transabdominal tap.

Special instructions
No ampoule file is needed to open the ampoules. The neck of the ampoule is prescored at the point of constriction. A colored dot on the ampoule head helps to orientate the ampoule. Take the ampoule and face the colored dot. The ampoule opens easily by placing the thumb on the colored dot and gently pressing downwards as shown.



OVERDOSAGE

Overdosage of dinoprost by the intra-amniotic route should result in accentuation of the normally occurring side effects of nausea, vomiting and diarrhea. Intravenous studies during clinical trials demonstrated that doses as high as 176.3 mg by intravenous infusion were tolerated but with severe nausea, vomiting, diarrhea and in some cases, hyperpyrexia.

Accidental intravascular injection of a bolus of dinoprost was suspected in two patients (see side effects above) and both tolerated these accidents. Dinoprost is very rapidly metabolized when given intravenously and this factor makes such massive doses safely tolerated.

Overdosage by the intra-amniotic route has not been reported. It would be expected that accentuated side effects might occur and the patient should be given supportive therapy (particularly intravenous fluid replacement), should serious vomiting and diarrhea occur.

Surgical rupture of the membranes with its associated loss of amniotic fluid should be considered at the appropriate time.

Although prostaglandin antagonists are known to exist, no experience has been obtained at the present time with their usage in cases of overdosage. Therefore, no specific therapy for overdosage is available.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Dinoprost has been shown to be luteolytic in the rat, rabbit, hamster, dog, rhesus monkey, cow and sheep, but not in the human female. In the human, dinoprost administered intra-amniotically stimulates the myometrium of the gravid uterus to contract in a manner similar to that seen in the uterus during labor.

Whether or not this action results from a direct effect of dinoprost on the myometrium has not been determined with certainty at this time. When dinoprost is injected into the amniotic sac, the amniotic fluid acts as a reservoir which slowly releases the drug so placed into the maternal circulation over a period of several hours, depending on the amount injected.

Dinoprost is also capable of stimulating the smooth muscle of the gastrointestinal tract in humans. This activity may be responsible for the vomiting and/or diarrhea that is not uncommon when dinoprost is used to terminate pregnancy.

In laboratory animals and also in humans, large doses of dinoprost can elevate blood pressure, probability as a consequence of its effect on the smooth muscle of the vascular system. In the doses used in the termination of a pregnancy, this effect has not been clinically significant.

STORAGE AND STABILITY

PROSTIN $F_{2\alpha}$ should always be stored at controlled room temperature (15-30 °C).

SPECIAL HANDLING INSTRUCTIONS

CAUTION: Spills of PROSTIN $F_{2\alpha}$ on the skin should immediately be washed off with soap and water to prevent absorption.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each milliliter of PROSTIN $F_{2\alpha}$ Sterile Solution contains 5mg dinoprost, 9 mg benzyl alcohol as a preservative and water for injection. Hydrochloric acid and/or sodium hydroxide may be present for pH adjustment.

PROSTIN $F_{2\alpha}$ (dinoprost) is available in cartons of 1 x 1 mL (5 mg) ampoules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

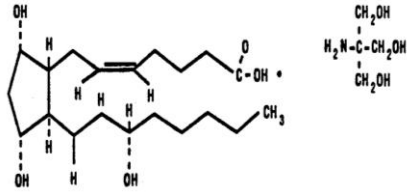
Drug Substance

Proper Name: dinoprost tromethamine

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

Molecular formula and molecular mass: $C_{20}H_{34}O_5.C_4H_{11}NO_3$
The molecular mass of dinoprost is 354.5 and that of dinoprost tromethamine is 475.6.

Structural Formula:



Physicochemical properties: Dinoprost tromethamine is a white or slightly off-white crystalline powder that is readily soluble in water at room temperature in concentrations to at least 200 mg/mL.

DETAILED PHARMACOLOGY

Animal Studies

Dinoprost has been investigated for its pharmacological activity in over one hundred animal in vivo experiments. Because of the dissimilarity between the animal estrus cycle and the human menstrual cycle, many of these experiments in animals, although scientifically of interest, have little application to the situation in the human pregnant female. Brief summaries are presented here of those studies considered to be of interest to the clinician.

Studies related to primary therapeutic activity

Dinoprost interrupts pregnancy in hamsters, rats, rabbits, mice and monkeys by many different routes of administration and at different stages of pregnancy. Uterine contractility is stimulated rapidly after administration to pregnant rhesus monkeys, intra-amniotically as well as by other routes.

Dinoprost was found to be luteolytic in most animal species, but not in the human. Abortions were induced in pregnant rhesus monkeys by injection of 1 or 5 mg of dinoprost into the amniotic sac. Contractions were maintained for a prolonged time and no detectable prostaglandin dehydrogenase activity was found in samples of amniotic fluid. These results indicate that the amniotic fluid apparently acts as a reservoir from which the drug is slowly released into the maternal uterine circulation.

Additional studies in monkeys indicated that by immunoassay the biological half-life (T½) in amniotic fluid is three to six hours as opposed to less than one minute in peripheral plasma. Plasma concentrations of prostaglandin following the intra-amniotic injection of ^{3}H-prostaglandin $F_{2\alpha}$ were maximal two hours following intra-amniotic injection, but significant amounts of radioactive prostaglandin were present for at least five additional hours.

Interactions between prostaglandins and oxytocin in animals are shown to be of two kinds. There may be potentiation where an increased response to oxytocin follows combination with a low dose of prostaglandin, and enhancement, which is of a much longer duration. Potentiation can be produced by both E and F prostaglandins, whereas enhancement is confined to E prostaglandins.

Prostaglandin $F_{2\alpha}$ was tested in immature female rats to measure its effect on gonadotropin activity. Neither ovarian weight gain nor ovulation were stimulated by prostaglandin $F_{2\alpha}$ administration. Prostaglandin $F_{2\alpha}$ did have an inhibiting effect on the results of PMS and HCG treatment, decreasing ovarian weight gain and ovulation. PMS stimulation of uterine growth was enhanced by prostaglandin $F_{2\alpha}$. This enhancement was probably due to increased secretion of estrogen by the ovary or by altering the ratio of estrogens to progestogens in the circulation.

Treatment of six <u>male</u> rhesus monkeys with 5 mg of prostaglandin $F_{2\alpha}$ indicated that there was no alteration of testicular steroidogenesis.

Studies of effect on the cardiovascular system

In rats, prostaglandin $F_{2\alpha}$ had no significant effect on cardiac output of the unanesthetized unrestrained rat. Blood pressure rose during the initial phase of the infusion, then fell to below control values and finally returned to pre-infusion measurements.

Prostaglandin $F_{2\alpha}$ infused at a rate of 10mcg/kg/min. caused significant increase in urine output, and sodium and chloride excretion.

In surgical preparations involving rhesus monkeys, subcutaneous injections of 15 mg of prostaglandin $F_{2\alpha}$ slightly increased cardiac output, pulmonary artery pressure, venous pressure and systemic arterial pressure, but heart rate was slightly decreased.

Prostaglandin $F_{2\alpha}$ is depressor in rabbits in contrast to its pressor action in rats, dogs and humans.

Studies of effect on the central nervous system

In male rats a 24-hour infusion of prostaglandin $F_{2\alpha}$ subcutaneously to a total dose of 1 mg/kg did not alter the utilization or turnover of catecholamines in the brain. <u>In vitro</u> prostaglandin $F_{2\alpha}$ at

10^{-3}M concentrations inhibited the phosphodiesterase of isolated synaptic vesicles from mouse brain by 58% but the significance of this inhibition has not yet been determined.

Studies of effect on the respiratory system
As a dose of 16.0 mcg/mL prostaglandin $F_{2\alpha}$ did not reverse SRS-A induced contractions of the guinea pig tracheal chain. The drug has nasal vasoconstrictor activity in an in vivo dog preparation, whether given by intra-carotid injection, or applied topically.

Studies of interaction of prostaglandin with other drugs
In general, there is no correlation between the ability of various psychotropic drugs to inhibit serum concentrations of prostaglandin $F_{2\alpha}$ and their apparent ability to inhibit acute inflammation. Drugs inhibiting prostaglandin $F_{2\alpha}$ synthesis in vitro are not necessarily effective when given in vivo. Non-steroidal anti-inflammatory drugs are effective on all parameters tested in vivo and in vitro. However, the observations that many anti-inflammatory drugs do inhibit prostaglandin synthesis may or may not explain their major mode of action.

Miscellaneous pharmacologic activities considered pertinent to efficacy and safety
Prostaglandin circulating in the peripheral blood of rats does so in the platelet. Inhibition of the circulating serum levels of the prostaglandins upon the administration of non-steroidal anti-inflammatory drugs is due almost entirely to their ability to inhibit platelet release machanisms upon activation of the clotting process. Their effects on platelets then are not related primarily to inflammation.

Metabolism

Animal Studies
After a single dose intra-amniotic injection in monkeys, the disappearance half-life for prostaglandin $F_{2\alpha}$ in amniotic fluid as measured by radioimmune assay ranged from 1.2 to 3.2 hours. Disappearance of drug-related materials as measured by total radioactivity following administration of tritium-labeled prostaglandin $F_{2\alpha}$ was estimated to be 6.8 hours. Plasma concentrations of prostaglandin $F_{2\alpha}$ and total radio-activity were maximal two hours post-intra-amniotic drug administration, and within four hours plasma concentrations had returned to pretreatment levels. But drug-related materials as measured by total radioactivity were in peripheral circulation upon termination of the study at seven hours. For comparison, peak levels were observed in monkeys in 30 seconds after single dose intravenous of 1 mg of the drug. Within 10 minutes serum concentrations had returned to pretreatment levels, suggesting rapid distribution, metabolism and/or excretion.

Studies of the distribution of tritium-labeled drug in mice using whole-body autoradiographic techniques showed that within five to 15 minutes after intravenous injection, most of the radioactivity was localized in liver, kidney and connective tissue and lower but significant uptake was found in lung tissue. No significant uptake was found in myocardium, brain, adipose tissue or endocrine glands. Greater than 90% of the administered dose was recovered in the urine and feces in 24 hours.

Human Studies

At six to ten hours after single-dose intra-amniotic administration of 40 mgms of prostaglandin $F_{2\alpha}$, peak drug concentrations of three to seven nanograms prostaglandin $F_{2\alpha}$ equivalents/mL were observed in peripheral circulation. Within 24 hours, blood concentrations had returned to near pretreatment levels.

After single dose parenteral administration of tritium-labeled drug in humans, urinary excretion of total radioactivity was very rapid, greater than 90% complete within 24 hours.

Investigations in pregnant and non-pregnant women showed no differences in the distribution or elimination of total radioactivity after a single dose intravenous administration of tritium-labeled prostaglandin $F_{2\alpha}$. No selective uterine uptake of drug-related materials was noted.

Measurement of total radioactivity in fetal tissue specimens indicated that drug and/or its metabolites were freely transported across the placenta. The relatively higher levels of radioactivity found in fetal liver, as compared to fetal lung, suggested a selective uptake of drug-related materials entering the liver directly via the umbilical vein and ductus venous.

The major urinary excretion product of prostaglandin $F_{2\alpha}$ in humans is 5α,7α-dihydroxy-11-keto-tetranorprosta-1,16-dioic acid.

TOXICOLOGY

Animal safety studies were done in variety of species by different routes of administration for varying periods of time.

Acute LD_{50} Studies of Dinoprost

Species	Sex	Route	LD_{50}
mice	male	I.V.	679 mg/kg
mice	female	I.V.	590 mg/kg

Rat Studies

Using prostaglandin $F_{2\alpha}$ base intravenously for 28 days at 3.2 mg/kg/day in rats, no evidence of toxicity was found. Single intraperitoneal injections of 5mg/kg in pre-parturient and new born rats likewise produced no toxicity. Continuous I.V. infusion of 16 mg/kg/day of the base for 14 days showed no evidence of toxicity.

Using dinoprost (prostaglandin $F_{2\alpha}$ THAM salt) orally in female rats at 0.5 and 5.0 mg/kg/day for five days, no pharmacological or toxicological effects were noted. When given continuously intravenously at 20 mg/kg/day for 14 days, dinoprost was pharmacologically active, but without specific organ toxicity.

In a reproduction study, female rats were treated via subcutaneous injection with doses of dinoprost at levels of 1.0 and 3.0 mg/animal/day for 14 days prior to breeding and at the same levels on days 9, 10 and 11 of gestation. Following a 28-day rest period, the females were re-mated to the same males and allowed to cast and keep their litters until weaning. The results of this study indicate that rats are capable of carrying out a normal pregnancy following treatment with dinoprost prior to and during the preceding pregnancy at dose levels which are embryocidal.

In a teratology study dinoprost produced a repeatable low incidence of costal and vertebral defects when administered at 0.5 and 1.0 mg/rat/day subcutaneously on gestation days 9, 10 and 11 to pregnant rats. These effects are probably due to fetal hypoxia as a result of uterine contractions and/or a specific decrease in uterine blood supply. No teratogenic effects were seen following dosing on gestation days 6, 7 and 8 or 12, 13 and 14.

Guinea Pig Studies

When administered intracutaneously to guinea pigs in gradually increasing doses over a 28-day period, dinoprost was not considered to have any anaphylactic sensitizing potential.

Rabbit Studies

Six rabbits given a single 1 mL intramuscular injection of prostaglandin $F_{2\alpha}$ base showed no evidence of muscle irritation. One rabbit revealed a moderate degree of hemorrhage and a trace of muscle degeneration at the injection site.

In a teratology study, pregnant rabbits received subcutaneous injections of dinoprost on either gestation days 6, 7 and 8 or 9, 10 and 11 or 12, 13 and 14 or 15, 16 and 17 at 0.5 or 1.0 mg/kg/day.

All groups so treated produced a significantly lower average number of live pups per litter and an increase in the average numbers of resorption sites per litter. Abortions were induced by both 0.5 and 1.0 mg/kg/day following treatment on gestation days 12, 13 and 14 or 15, 16 and 17. In these litters which did not abort after treatment on days 15, 16 and 17, no other adverse effects on reproduction were noted. The appearance of a combination of malformations and the repetition of single malformations in fetuses from different dinoprost-treated litters suggests teratogenic activity in this species under the conditions of this study.

Dog Studies

A dosage of 0.6 mg/kg/day of prostaglandin $F_{2\alpha}$ base intravenously in dogs for a period of 30 days produced no signs of toxicity.

In a five-day oral toxicity study at doses of 10 and 30 mg/kg/day, dinoprost was judged to be pharmacologically active and non-toxic.

Monkey Studies

Prostaglandin $F_{2\alpha}$ (base compound) was administered by continuous I.V. infusion to monkeys for two weeks at a rate of 15mg/kg/day. The compound was not considered to be toxic in this experiment. Changes that may have been associated with its administration were (1) Reduced circulating lymphocytes; (2) Slight increase in blood urea nitrogen; (3) Slight lowering of blood cholesterol levels; and (4) Some increase in blood fibrinogen levels. In a similar experiment at a dose level of 20 mg/kg/day, no significant clinical or toxicological effects were noted.

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PART III: CONSUMER INFORMATION

PROSTIN $F_{2\alpha}$
Dinoprostone Tromethamine
Prostaglandin

This leaflet is part III of a three-part "Product Monograph" published when PROSTIN $F_{2\alpha}$ 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 $F_{2\alpha}$. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PROSTIN $F_{2\alpha}$ is used to induce labour in pregnant women in the second trimester.

What it does:
PROSTIN $F_{2\alpha}$ 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 $F_{2\alpha}$ should not be used if:

- You are allergic to prostaglandins or any oxytocic drug or any of the other ingredients in **PROSTIN $F_{2\alpha}$**;
- You have or have had untreated pelvic inflammatory disease;
- You are having heart, lung, kidney or liver disease.

What the medicinal ingredient is:
PROSTIN $F_{2\alpha}$ (dinoprost tromethamine) is available as 1 mL (5 mg) ampoules

What the nonmedicinal ingredients are:
Benzyl alcohol (preservative), hydrochloric acid, sodium hydroxide and water for injection

What dosage forms it comes in:
PROSTIN $F_{2\alpha}$ is a white or slightly off-white crystalline powder.

Each syringe contains:
5 mg dinoprost /1.0 mL ampoule (closed glass container)

WARNINGS AND PRECAUTIONS

PROSTIN $F_{2\alpha}$ should be given to you by doctor experienced in using the drug.

BEFORE you use PROSTIN $F_{2\alpha}$ 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 heart, liver, kidney problem.

Pregnancy: **PROSTIN $F_{2\alpha}$** may cause birth defects. Therefore, a pregnancy diagnosed as a missed abortion should be ended by some other means. Benzyl alcohol (preservative) can cross the placenta and may be harmful to the unborn child.

INTERACTIONS WITH THIS MEDICATION

Before receiving **PROSTIN $F_{2\alpha}$** tell your doctor if you are taking other drugs, including non-prescription and natural health products.

PROPER USE OF THIS MEDICATION

Usual dose:
A trained obstetrical staff will perform a transabdominal tap of the amniotic sac. **PROSTIN $F_{2\alpha}$** will then be injected intra-amniotically.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In most commonly events observed with the use of **PROSTIN $F_{2\alpha}$** were vomiting (57.1%), nausea (24.8%), and diarrhea (16.1%).

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**	
Un-Common	**Rupture of upper intervaginal cervix**		√	
	Ruptured uterus		√	
	Convulsions		√	
	Severe reaction affecting the body		√	
	Intra-uterine infection		√	

This is not a complete list of side effects. For any unexpected effects while taking PROSTIN $F_{2\alpha}$, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15-30 °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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