PRODUCT MONOGRAPH

PrCERVIDIL*

Dinoprostone
10 mg Vaginal Insert

Prostaglandin

Ferring Inc.
200 Yorkland Blvd., Suite # 800
Toronto, Ontario
M2J 5C1

Date of Preparation:
April 1, 1997

Date of Revision:
September 29, 2006

Control Number : 107457

Table of Contents

CERVIDIL

dinoprostone

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Vaginal	10 mg	Hydrogel Polymer Prepared with: Macrogol 8000 Dicyclohexylmethane-4,4'diisocyanate 1,2,6-Hexanetriol Polyester Retrieval system

INDICATIONS AND CLINICAL USE

Cervdil (dinoprostone) is indicated for:

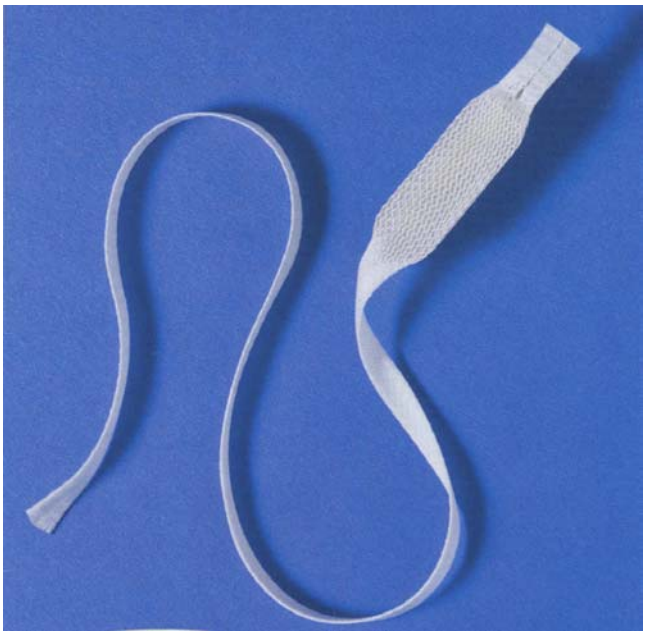
- Initiation and/or continuation of cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labour.

Geriatrics (> 65 years of age):
Cervidil has not been studied in this patient population and is not recommended for use.

Pediatrics (< 18years of age):
Cervidil has not been studied in this patient population and is not recommended for use.

DESCRIPTION OF VAGINAL INSERT

CERVIDIL is a thin, flat, semi-transparent polymeric slab which is rectangular in shape with rounded corners contained within a knitted polyester retrieval system, as illustrated below.



Each insert contains 10 mg dinoprostone (prostaglandin E_2) dispersed throughout its matrix, and releases approximately 0.3 mg/hour PGE_2 over a 12 hour period. The reservoir of 10 mg dinoprostone serves to maintain constant release.

The retrieval system consists of a one-piece knitted polyester pouch and withdrawal tape. This ensures easy and reliable removal of the insert when the patient's requirement for PGE_2 has been fulfilled or an obstetric event makes it necessary to stop further drug administration.

CONTRAINDICATIONS

CERVIDIL is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients in whom there is clinical suspicion or definite evidence of fetal distress where delivery is not imminent;
- Patients with placenta previa or unexplained vaginal bleeding during this pregnancy;
- Patients in whom there is evidence or strong suspicion of marked cephalopelvic disproportion;
- Patients in whom oxytocic drugs are contraindicated or when prolonged contraction of the uterus may be detrimental to fetal safety or uterine integrity (previous cesarean section or major uterine surgery);
- Multipara with 6 or more previous term pregnancies;
- Patients with a history of difficult labour and/or traumatic delivery;
- Patients with overdistension of uterus (multiple pregnancy, polyhydramnios);
- Patients with fetal malpresentation;
- Patients with a history of epilepsy whose seizures are poorly controlled;
- CERVIDIL should not be used simultaneously with other oxytocics; (See Warnings)
- CERVIDIL should not be used when there is a history of, or current pelvic inflammatory disease, unless adequate prior treatment has been instituted.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

For Hospital Use Only:

Cervidil should be administered only by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities.

General

Since prostaglandins potentiate the effect of oxytocin, CERVIDIL must be removed before oxytocin administration is initiated and the patient's uterine activity carefully monitored for uterine hyperstimulation.

If uterine hyperstimulation is encountered or if labour commences, the vaginal insert should be removed. CERVIDIL should also be removed prior to amniotomy. The vaginal insert should be removed if there is evidence of maternal systemic adverse PGE_2 effects such as nausea, vomiting, hypotension or tachycardia.

The experience of CERVIDIL® in patients with ruptured membranes is limited. Therefore, CERVIDIL® should be used with caution in those patients. Since the release of dinoprostone from the insert can be affected in the presence of amniotic fluid, special attention should be given to uterine activity and fetal condition.

Caution should be exercised in the administration of CERVIDIL for cervical ripening in patients with a history of previous uterine hypertonicity, glaucoma, or a history of childhood asthma, even though there have been no asthma attacks in adulthood or unexplained genital bleeding during the current pregnancy.

Women aged 35 and over (occasionally also younger women), women with complications during pregnancy and women at gestational age above 40 weeks, have a higher risk for developing disseminated intravascular coagulation (DIC). These factors may enhance the risk of disseminated intravascular coagulation in women with pharmacologically induced labour.

Therefore, dinoprostone should be used with caution in these women. In the immediate post-partum phase the physician should look carefully for early signs of developing DIC (e.g. fibrinolysis).

Uterine activity, fetal status and the progression of cervical dilatation and effacement should be carefully monitored whenever the dinoprostone vaginal insert is in place. Any evidence of uterine hyperstimulation, sustained uterine contractions, fetal distress, or other fetal or maternal adverse reactions, should be a cause for consideration of removal of the insert. The possibility of uterine rupture and/or cervical laceration should be born in mind where hypertonic myometrial contractions are sustained.

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

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.

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

Carcinogenesis and Mutagenesis

Long-term carcinogenicity and fertility studies have not been conducted with CERVIDIL (dinoprostone vaginal insert). No evidence of mutagenicity has been observed with prostaglandin E_2 in the Unscheduled DNA Synthesis Assay, the Micronucleus Test, or Ames Assay.

Special Populations

Pregnant Women:
Animal studies indicate that the prostaglandins may be teratogenic. No effect would be expected clinically, when used as indicated, since CERVIDIL (dinoprostone vaginal insert) is

administered after the period of organogenesis. Any dose of the drug that produces sustained increased uterine tone could put the embryo or fetus at risk.

Nursing Women:

Cervidil is not indicated for use during early or other phases of pregnancy or during lactation.

Monitoring and Laboratory Tests

After insertion, the patient should remain supine and monitored for 2 hours for any evidence of uterine hyperstimulation, change in fetal heart rate or maternal blood pressure or heart rate.

If any of these changes occur, removal of Cervidil should be considered.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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*.

CERVIDIL is well tolerated. In placebo-controlled trials in which 658 women were entered and 320 received active therapy (218 without retrieval system, 102 with retrieval system), the following events were reported.

Table 1

Total Drug Related Adverse Events

	Controlled Studies[1]		*Study 101-801*[2]	
	Active	*Placebo*	*Active*	*Placebo*
Uterine hyperstimulation with fetal distress	*2.8%*	*0.3%*	*2.9%*	*0%*
Uterine hyperstimulation without fetal distress	*4.7%*	*0%*	*2.0%*	*0%*
Fetal Distress without uterine hyperstimulation	*3.8%*	*1.2%*	*2.9%*	*1.0%*
N	*320*	*338*	*102*	*104*

[1] Controlled Studies (with and without retrieval system)

[2] Controlled Study (with retrieval system)

Drug related fever, nausea, vomiting, diarrhea, and abdominal pain were noted in less than 1% of patients who received CERVIDIL.

The following table outlines the frequency of reported adverse events:

Frequency	**MedDRA System Organ Class**	**Adverse Events (MedDRA Preferred Term)**
Common (>1/100, <1/10)	Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting fetus Fetal heart rate disorder Fetal distress syndrome Uterine hypertonus
Uncommon (>1/1,000, <1/100)	Gastro-intestinal disorders	Nausea, vomiting, diarrhea
Rare (>1/10,000, <1/1,000)	Blood and lymphatic system disorders Reproductive system and breast disorders Pregnancy, puerperium and perinatal conditions	Disseminated intravascular coagulation Uterine rupture

An increased risk of post-partum disseminated intravascular coagulation has been reported in patients whose labour was induced by pharmacological means, either with dinoprostone or oxytocin.The frequency of this adverse event, however, appears to be rare (<1 per 1,000 pregnancies).

Very rare cases of anaphylactic reactions have been reported with the use of dinoprostone.

In Study 101-801 (with the retrieval system) all cases of hyperstimulation reversed within 2 to 13 minutes of removal of the product. Tocolytics were required in one of the five cases.

In cases of fetal distress, when product removal was thought advisable, there was a return to normal rhythm and no neonatal sequelae.

Five minute Apgar scores were 7 or above in 98.2% (646/658) of studied neonates whose mothers participated in placebo-controlled studies with CERVIDIL. A 3 year pediatric follow-up study in 121 infants whose mothers received PGE_2, found no significant differences from a control group on physical examination or psychomotor evaluation.

Post-Market Adverse Drug Reactions:

In post marketing experience reports, uterine rupture has been reported rarely in association with the use of Cervidil (see Warning and Precautions and Contraindications sections).

DRUG INTERACTIONS

Overview

CERVIDIL may augment the activity of oxytocic agents and their concomitant use is not recommended. A dosing interval of at least 30 minutes is recommended for the sequential use of oxytocin following the removal of the dinoprostone vaginal insert. No other drug interactions have been identified.

DOSAGE AND ADMINISTRATION

To remove Cervidil from the packaging, first tear the foil along the top of the sachet. Do not use scissors or sharp implements to cut the foil as this may damage the product. Use the retrieval system to gently pull the product out of the sachet.

After removal from the patient, ensure that the entire product (vaginal delivery system and retrieval system) has been removed from the vagina.

Recommended Dose and Dosage Adjustment

The dosage of dinoprostone in the vaginal insert is 10 mg designed to be released at approximately 0.3 mg/hour over a 12 hour period. CERVIDIL should be removed upon onset of active labour or 12 hours after insertion.

One CERVIDIL is placed transversely in the posterior fornix of the vagina immediately after removal from its foil package. The insertion of the vaginal insert does not require sterile conditions. The vaginal insert must not be used without its retrieval system. There is no need for previous warming of the product. A minimal amount of K-Y® jelly (or other water-miscible lubricant) may be used to assist in insertion of CERVIDIL. Care should be taken not to permit excess contact or coating with the lubricant and thus prevent optimal swelling and release of dinoprostone from the vaginal insert. Patients should remain in the supine position for 2 hours following insertion, but thereafter may be ambulatory.

OVERDOSAGE

CERVIDIL is used as a single dosage in a single application. Overdosage is usually manifested by uterine hyperstimulation which may be accompanied by fetal distress and is responsive to removal of the insert. Other treatment must be symptomatic, since to date, clinical experience with prostaglandin antagonists is insufficient.

The use of beta-adrenergic agents should be considered in the event of undesirable increased uterine activity

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Dinoprostone (PGE_2) is a naturally-occurring biomolecule. It is found in low concentrations in most tissues of the body and functions as a local hormone. As with any local hormone, it is very rapidly metabolized in the tissues of synthesis. The rate limiting step for inactivation is regulated by the enzyme 15-hydroxyprostaglandin dehydrogenase (PGDH). Any PGE_2 that escapes local inactivation is rapidly cleared to the extent of 95% on the first pass through the pulmonary circulation.

In pregnancy, PGE_2 is secreted continuously by the fetal membranes and placenta and plays an important role in the final events leading to the initiation of labour. It is known that PGE_2 stimulates the production of $PGF_{2\alpha}$ which in turn sensitizes the myometrium to endogenous or exogenously administrated oxytocin. Although PGE_2 is capable of initiating uterine contractions and may interact with oxytocin to increase uterine contractility, the available evidence indicates, that in the concentrations found during the early part of labour, PGE_2 plays an important role in cervical ripening without affecting uterine contractions. This distinction serves as the basis for considering cervical ripening and induction of labour, usually by the use of oxytocin, as two separate processes.

PGE_2 plays an important role in the complex set of biochemical and structural alterations involved in cervical ripening. Cervical ripening involves a marked relaxation of the cervical smooth muscle fibers of the uterine cervix which must be transformed from a rigid structure to a softened, yielding and dilated configuration to allow passage of the fetus through the birth canal. This process involves activation of the enzyme collagenase, which is responsible for digestion of some of the structural collagen network of the cervix. This is associated with a concomitant increase in the amount of hydrophilic glycosaminoglycan, hyaluronic acid, and a decrease in dermatan sulfate. Failure of the cervix to undergo these natural physiologic changes, usually assessed by the method described by Bishop, prior to the onset of effective uterine contractions, results in an unfavourable outcome for successful vaginal delivery and may result in fetal compromise. It is estimated that in approximately 5% of the pregnancies the cervix does not ripen normally. In an additional 10-11% of pregnancies, labour must be induced for medical or obstetric reasons prior to the time of cervical ripening.

Pharmacodynamics

Pharmacotherapeutic group: oxytocics.

Prostaglandin E_2 (PGE_2) is a naturally occurring compound found in low concentrations in most tissues of the body. It functions as a local hormone.

Prostaglandin E_2 plays an important role in the complex set of biochemical and structural alterations involved in cervical ripening. Cervical ripening involves a marked relaxation of the cervical smooth muscle fibres of the uterine cervix which must be transformed from a rigid structure to a soft, dilated configuration to allow passage of the fetus through the birth canal. This process involves activation of the enzyme collagenase which is responsible for the breakdown of the collagen.

Local administration of dinoprostone to the cervix results in cervical ripening which then induces the subsequent events which complete labour

Pharmacokinetics

PGE_2 is rapidly metabolised primarily in the tissue of synthesis.

No correlation could be established between PGE_2 release and plasma concentrations of its metabolite, PGE_m. The relative contributions of endogenously and exogenously released PGE_2 to the plasma levels of the metabolite PGE_m could not be determined.

The reservoir of 10 mg dinoprostone serves to maintain a controlled and constant release. The release rate is approximately 0.3 mg per hour over 12 hours in women with intact membranes whereas release is higher and more variable in women with premature rupture of membranes. Cervidil releases dinoprostone to the cervical tissue continuously at a rate which allows cervical ripening to progress until complete, and with the facility to remove the dinoprostone source when the clinician decides that cervical ripening is complete or labour has started, at which point

no further dinoprostone is required.

STORAGE AND STABILITY

Store in a freezer between -20^{o}C and -10^{o}C

DOSAGE FORMS, COMPOSITION AND PACKAGING

CERVIDIL (dinoprostone 10 mg vaginal insert) is available in a carton containing 1 insert within a retrieval system, enclosed in foil (aluminium/polyethylene) pack.

Each insert contains 10 mg of dinoprostone in 236 mg of a cross-linked polyethylene oxide/urethane polymer which is a semi-transparent, beige coloured, flat, 0.8 mm thick rectangular slab measuring 29 mm by 9.5 mm. The insert and its retrieval system, is made of polyester yarn, are non-toxic and when placed in a moist environment, absorbs water, swells, and releases dinoprostone.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Dinoprostone

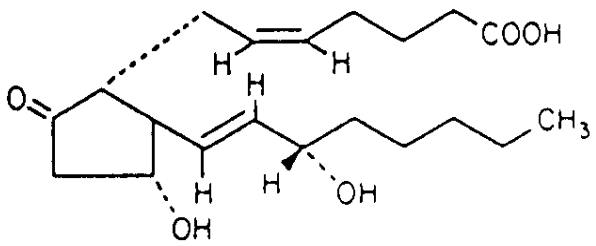
Chemical Names:

(1)Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-,(5*Z*,11α,13*E*,-15*S*)-

(2)(*E*,*Z*)-(1*R*,2*R*,3*R*)-7-[3-Hydroxy-2-[(3*S*)-(3-hydroxy-1-octenyl)]-5-oxocyclopentyl]-5-heptenoic acid

(3) Prostaglandin E_2

Structural Formula:



Molecular Formula:

$C_{20}H_{32}O_5$

Molecular Weight:

352.47

DESCRIPTION:

Dinoprostone occurs as a white to off-white crystalline powder. It has a melting point within the range of 65° to 68°C. Dinoprostone is freely soluble in ethanol, methylene chloride, ethyl acetate and chloroform, and very slightly soluble in n-hexane. Aqueous solubility is 1.05 mg/mL at 25°C.

COMPOSITION

Each insert contains 10 mg of dinoprostone in 236 mg of a cross-linked polyethylene oxide/urethane polymer which is a semi-transparent, beige coloured, flat, 0.8 mm thick rectangular slab measuring 29 mm by 9.5 mm. The insert and its retrieval system, made of polyester yarn, are non-toxic and when placed in a moist environment, absorb water, swell, and release dinoprostone.

TOXICOLOGY

Toxicology studies have been conducted on PGE_2, on the hydrogel polymer and on the insert retrieval system.

There is little information specifically related to PGE_2 toxicity because of its rapid inactivation in the body. A study in chicken embryos and newly hatched chicks showed that there was no discernable PGE_2-related lethality following administration of doses between 10^{-5} and 10^{-8}M to embryos and proportionally larger doses to chicks.

The hydrogel polymer showed no evidence of toxicity in a cytotoxicity study in mouse fibroblast cultures or in an intramuscular implantation test in rabbits. Dietary and oral toxicity studies of the hydrogel polymer in rats and dogs were conducted for periods between 10 and 36 days and showed no evidence of toxicity.

In vitro unscheduled DNA synthesis assays on primary rat hepatocytes showed no evidence of mutagenicity for PGE_2 at doses up to 5000 μg/mL.

PGE_2 administered subcutaneously to female mice at doses up to 50 μg/kg/day during days 11 to 17 of pregnancy had a masculinizing effect on the genital tract of female fetuses. The results of this study and a related *in vitro* study using female genital duct cultures suggest that PGE_2 plays a role in androgen-dependent masculine differentiation.

The insert retrieval system which is composed of the polyester material Dacron T56 and the material itself were evaluated in *in vitro* cytotoxicity tests, systemic toxicity tests in mice, intramuscular implantation tests in rabbits, hemolysis tests, pyrogenicity tests, intracutaneous reactivity tests in rabbits, skin irritation tests in guinea pigs and vaginal irritation tests in rabbits. There was no evidence of toxicity in any of the studies.

The results of an *in vitro* test using *Staphylococcus aureus* predict no association between the use of the hydrogel insert and toxic shock syndrome.

REFERENCES

1. Physiology of labor. In: Pritchard JA, MacDonald PC, Gant NF, eds. Williams Obstetrics. Appleton Century Crofts, Norwalk, CN. 1985; 295-321.

2. Casey ML, MacDonald PC, Mitchell MD. Stimulation of prostaglandin E_2 production in amnion cells in culture by a substance(s) in human fetal urine. Biochem Biophys Res Comm 1983; 114: 1056-1063.

3. Cibils LA. Enhancement of induction of labor. In: Aladjem S, ed. Risks in the Practice of Modern Obstetrics. Mosby Publishing, St. Louis 1972; 182-209.

4. Thiery M. Induction of labor with prostaglandins. In: Keirse MJNC, Anderson ABM, Graven-horst JB, eds. Human Parturition. Martinus Nijhoff Publ., Boston, 1979; 155-164.

5. Amy JJ, Thiery M. Induction of labor with prostaglandins. In: Karim SMM, ed. Advances in Prostaglandin Research. Prostaglandins and Reproduction. MTP Press, Lancaster, 1979; 437-446.

6. Bishop E. Pelvic scoring for elective induction. Obstet & Gynecol 1964; 24: 266-268.

7. Thiery M. Preinduction cervical ripening. In: Wynn RM, ed. Obstetrics and Gynecology Annual, Vol. 12. Appleton-Century-Crofts, New York, 1983; 103-146.

8. Westgate J, Williams JA. Evaluation of a controlled release vaginal prostaglandin E_2 pessary with retrieval system for the induction of labour. Journal of Obstetrics and Gynecology 1994; 14: 146- 150.

9. Witter FR, Critical drug appraisal: Sustained release dinoprostone - effective therapy for cervical ripening at term. Pharmacy and Therapeutics December 1995.

10. Rayburn WF, Wapner RJ, Barss VA, Spitzberg E, Molina RD, Mandsager N, Yonekura ML. An intravaginal controlled-release prostaglandin E_2 pessary for cervical ripening and initiation of labour at term. Obstetrics & Gynecology 1992; 79: 374-379.

11. Smith CV, Rayburn WF, Miller AM. Intravaginal prostaglandin E2 for cervical ripening and initiation of labour. Reprod Med 1994; 39: 381-384.

PART III: CONSUMER INFORMATION

Cervidil®

dinoprostone, 10 mg vaginal insert

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

ABOUT THIS MEDICATION

What the medication is used for:

Cervidil is used to start or continue "cervical ripening" in patients at the end of pregnancy when there is a medical or obstetrical reason to induce labour.

What it does:

Cervidil ripens the cervix (opening of the uterus) in patients at the end of pregnancy where there is a medical or obstetrical reason for the induction of labour. Cervical ripening describes the changes in the cervix during the final weeks of normal pregnancy when the cervix gradually becomes softer, more flexible, stretchy, and shorter.

When it should not be used:

Cervidil should not be used or left in place;

- When labour has started
- When there is a known sensitivity to prostaglandins (Cervidil is a prostaglandin which is like a hormone in the body)
- When there is a suspicion or evidence of a problem with the baby and delivery will not be soon
- When the placenta is attached close to or covering the cervix (opening into the uterus) or there is unexplained vaginal bleeding during this pregnancy
- When there is evidence or strong suspicion that the baby's head is too large to fit through the mother's pelvis
- When drugs used to stimulate labour are not indicated or when prolonged contraction of the uterus may be harmful to the baby's safety or stability of the uterus (previous cesarean section or major uterine surgery)
- When there have been many pregnancies (6 or more previous term pregnancies)
- When there is a history of difficult labour and/or delivery
- When the uterus is very large (multiple pregnancy, too much amniotic fluid around the baby)
- When the baby is not in the correct position to deliver properly head first
- When there is a history of epilepsy and seizures are poorly controlled
- When other drugs are being given to stimulate labour (See Warnings)
- When there is a history of, or current pelvic inflammatory disease (infection or inflammation of the uterus, fallopian tubes, and ovaries) unless adequate prior treatment has been given

What the medicinal ingredient is:

Dinoprostone

What the important nonmedicinal ingredients are:

Hydrogel Polymer
Prepared with:
Macrogol 8000
Dicyclohexylmethane-4,4'diisocyanate

1,2,6-Hexanetriol

Polyester Retrieval system

What dosage forms it comes in:

Vaginal Insert, 10 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

For Hospital Use Only:

Cervidil should be administered only by trained obstetrical staff in a hospital setting with appropriate obstetrical care facilities.

BEFORE you use Cervidil please talk to your doctor:

- Since prostaglandins increase the effect of other drugs used to stimulate labour, Cervidil must be removed before another drug to stimulate labour is started and your uterine activity should be carefully monitored for uterine overstimulation.

- If excessive stimulation of the uterus occurs or if labour starts, Cervidil should be removed. Cervidil should also be removed before artificial tearing of the membranes to induce or speed up labour. Cervidil should be removed if you experience any adverse effects such as nausea, vomiting, lowered blood pressure or an abnormal rapid heart rate.

- The experience of Cervidil in patients with ruptured membranes is limited. Therefore, Cervidil should be used with caution in those patients. Since the release of dinoprostone from Cervidil can be affected in the presence of amniotic fluid, special attention should be given to uterine activity and the baby's condition.

- Your doctor should use caution using Cervidil for cervical ripening if you have a history of previous uterine overactivity, glaucoma (increased pressure in the eyes), or a history of childhood asthma, even though there have been no asthma attacks in adulthood.

- Women aged 35 and over (occasionally also younger women), women with complications during pregnancy and women with a pregnancy of more than 40 weeks, have a higher risk for developing a generalized blood clotting disorder. The risk of this blood clotting disorder may be higher in women with induced labour. Therefore, dinoprostone and other drugs used to stimulate labour should be used with caution in these women. Immediately after the delivery the physician should

look carefully for early signs of developing this clotting disorder.

- Uterine activity, status of the baby and the progression of cervical dilatation and shortening should be carefully monitored whenever Cervidil is in place. If there is any evidence of uterine overstimulation, sustained uterine contractions, problems with the baby, or other adverse reactions concerning the mother or baby removal of the insert should be considered. The possibility of uterine rupture and/or cervical tearing should be considered when very strong contractions are sustained.

- The size of the baby's head compared to your pelvis should be carefully evaluated before the use of Cervidil.

- There are different types of prostaglandins. Prolonged treatment of newborn infants with a prostaglandin E_1 may affect bone growth. There is no evidence that short term administration of prostaglandin E_2 (Cervidil) can cause similar bone effects.

- Patients with severe kidney disease and/or severe liver disease accompanied by metabolic abnormalities should be treated with caution. Make sure your doctor knows if you have any health problems.

INTERACTIONS WITH THIS MEDICATION

Cervidil may increase the activity of other drugs used to stimulate labour and their use at the same time is not recommended. A waiting period of at least 30 minutes is recommended before the use of other drugs used to stimulate labour following the removal of Cervidil. No other drug interactions have been identified.

PROPER USE OF THIS MEDICATION

To remove Cervidil from the packaging, first tear the foil along the top of the sachet. Do not use scissors or sharp implements to cut the foil as this may damage the product. Use the retrieval system to gently pull the product out of the sachet.

After removal from the patient, ensure that the entire product (vaginal delivery system and retrieval system) has been removed from the vagina.

Usual dose:
The dosage of dinoprostone in Cervidil is 10 mg, designed to be released at approximately 0.3 mg/hour over a 12 hour period. Cervidil should be removed upon onset of active labour or 12 hours after insertion.
One Cervidil is placed in the space behind the cervix immediately after removal from its foil package. The insertion of Cervidil does not require sterile conditions. Cervidil must not be used without its retrieval system. There is no need for previous warming of the product. A minimal amount of K-Y® jelly (or other water-based lubricant) may be used to assist in insertion of Cervidill. Care should be taken to prevent excess contact or coating with the lubricant and thus prevent optimal swelling and release of dinoprostone from Cervidil. You should remain lying on your back for 2 hours following insertion, but you can then be up and about.

Overdose:

Cervidil is used once only. An overdose is usually shown by strong uterine contractions. If an overdose is suspected, Cervidil can be removed easily by pulling on the retrieval string.

If any prolonged increased uterine activity occurs, the use of medication to treat these undesirable effects should be considered.

Missed Dose:
N/A

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Cervidil is well tolerated. In studies in which 658 women were treated and 320 received active therapy (218 without retrieval system, 102 with retrieval system), the following events were reported: Out of 102 patients five (4.9%) had uterine overstimulation. Of these, three (2.9%) of the cases were associated with fetal distress. Of the five cases, four resolved after the removal of Cervidil.

Drug related fever, nausea, vomiting, diarrhea, and abdominal pain were noted in less than 1% of patients who received Cervidil

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 heart rate disorder		✓	
	Fetal distress syndrome		✓	
	Uterine hypertonus		✓	
Uncommon	Nausea, vomiting, diarrhea		✓	✓

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

HOW TO STORE IT

Store in a freezer between -20°C and -10°C

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Ferring Inc., at: 1-800-263-4057

This leaflet was prepared by Ferring Inc.

FERRING
PHARMACEUTICALS

Last revised: September 29, 2006