

CERVIDIL- dinoprostone insert

Ferring Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CERVIDIL safely and effectively. See full prescribing information for CERVIDIL.

CERVIDIL® (dinoprostone) vaginal insert
Initial U.S. Approval: 1977

INDICATIONS AND USAGE

CERVIDIL is a prostaglandin analog indicated for the initiation and/or continuation of cervical ripening in pregnant women at or near term in whom there is a medical or obstetrical indication for the induction of labor. (1)

DOSAGE AND ADMINISTRATION

- Administer a single vaginal insert (10 mg) for up to 12 hours of use (approximately 0.3 mg of dinoprostone is released per hour) (2.1)
- Remove upon onset of active labor or 12 hours after insertion. (2.1)
- Carefully monitor for uterine activity, fetal status and the progression of cervical dilatation and effacement. (2.1)
- CERVIDIL should be administered only by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities (2.2).
- See full prescribing information for complete preparation, administration, and removal instructions. (2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

Vaginal Insert: 10 mg of dinoprostone contained within a knitted polyester pouch retrieval system. (3)

CONTRAINDICATIONS

CERVIDIL is contraindicated for:

- Known hypersensitivity to prostaglandins (4)
- Evidence or clinical suspicion of fetal distress, where delivery is not imminent (4)
- Unexplained vaginal bleeding in the current pregnancy (4)
- Evidence or clinical suspicion of marked cephalopelvic disproportion (4)
- Contraindication to induction of labor (4)
- Concurrent use with intravenous oxytocic agents (4)
- History of previous cesarean section or other uterine surgery (such as myomectomy) (4)
- Conditions under which prolonged contraction of the uterus may be detrimental to fetal safety. (4)
- Six or more previous term pregnancies (4)

WARNINGS AND PRECAUTIONS

- Disseminated Intravascular Coagulation: Assess for evolving fibrinolysis in the immediate post-partum period. (5.2)
- Amniotic Fluid Embolism Syndrome: Carefully monitor patients for clinical signs of hypotension, hypoxemia and respiratory failure, DIC, coma or seizures. Provide supportive care. (5.3)
- Uterine Tachysystole and Uterine Hypersystole/Hypertonicity: Monitor uterine activity; remove vaginal insert. (5.4)
- History of Glaucoma: Consider non-prostaglandin cervical ripening procedures. (5.5)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 2\%$) are uterine tachysystole without fetal distress, uterine tachysystole with fetal distress, and fetal distress without uterine tachysystole. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact FERRING PHARMACEUTICALS, INC. at 1-888-FERRING (1-888-337-7464) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Oxytocic Agents: May augment the activity of oxytocic agents; concomitant use of intravenous oxytocic agents is contraindicated (4, 7.1). Remove vaginal insert at least 30 minutes before administering an oxytocic agent. (7.1)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CERVIDIL is indicated for the initiation and/or continuation of cervical ripening in pregnant women at or near term in whom there is a medical or obstetrical indication for the induction of labor.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Instructions

Administer one CERVIDIL insert (10 mg) intravaginally for use up to 12 hours (approximately 0.3 mg of dinoprostone is released per hour) [see *Dosage and Administration* (2.2)].

Monitor uterine activity, fetal status, and the progression of cervical dilatation and effacement with the use of CERVIDIL. Remove CERVIDIL 12 hours after insertion with the onset of active labor, prior to an amniotomy, occurrence of uterine tachysystole, uterine hypersystole/hypertonicity, or fetal distress [see *Warnings and Precautions* (5.4)]. Remove CERVIDIL at least 30 minutes prior to administering an oxytocic agent [see *Warnings and Precautions* (5.4) and *Drug Interactions* (7)].

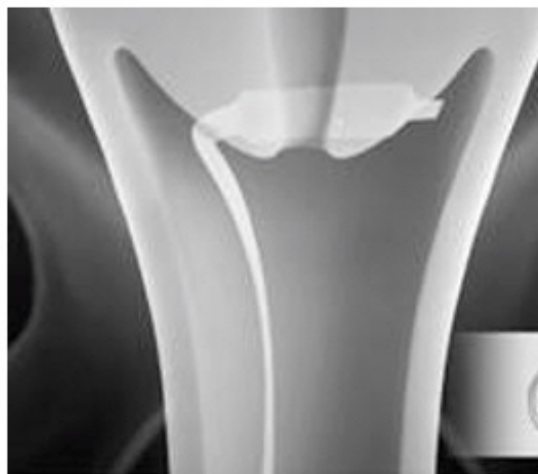
2.2 Preparation and Administration Instructions

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

Preparation and Administration Instructions

- Keep CERVIDIL frozen until ready for use. Do not warm CERVIDIL prior to vaginal insertion.
- Tear open the individually-wrapped foil package containing CERVIDIL along the tear mark. Never open the package using scissors or other sharp objects because this may damage the knitted polyester retrieval system. Do not cut the retrieval system and do not use CERVIDIL unless its retrieval system is intact.
- Immediately after opening the package, insert CERVIDIL transversely, in the posterior fornix of the vagina (see Figure 1). If necessary, use a minimal amount of water-miscible lubricant to assist vaginal insertion. Do not permit excess contact or coating with the lubricant, as this could prevent release of dinoprostone from the vaginal insert. Insertion does not require sterile conditions.

Figure 1: Placement of CERVIDIL in the Posterior Vaginal Fornix



- Tuck some of the excess retrieval system into the vagina to avoid movement of CERVIDIL away from the proper position; however, leave a small amount of the retrieval system outside the vagina to aid in retrieval.
- Instruct women to remain in a recumbent position during insertion of CERVIDIL and for 2 hours afterward. Women may be ambulatory 2 hours after insertion; however, ensure that the insert remains in place.

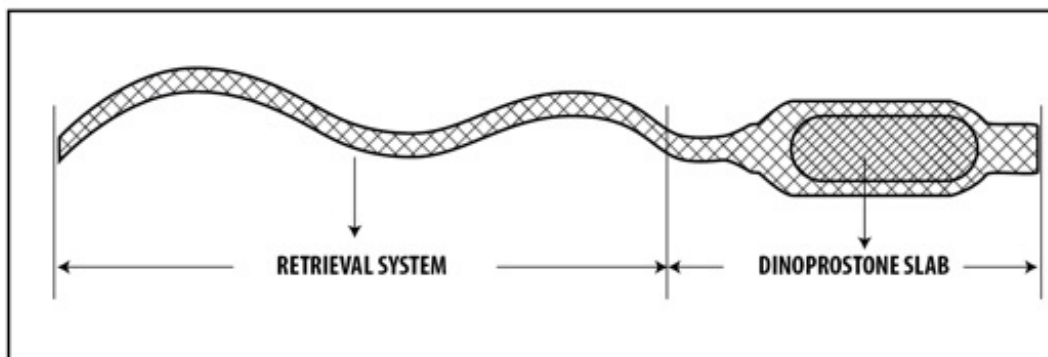
2.3 Removal Instructions

- To retrieve, locate the retrieval system and pull it gently until CERVIDIL is fully removed.
- Upon removal of CERVIDIL, it is essential to perform a visual inspection to ensure that the slab has been removed, as it will continue delivering the active ingredient.

3 DOSAGE FORMS AND STRENGTHS

Vaginal Insert: 10 mg of dinoprostone (release rate approximately 0.3 mg/hour up to 12 hours) in a hydrogel polymer. The insert is beige-colored, semi-opaque, thin, flat, and rectangular in shape with rounded corners, measuring 29 mm by 9.5 mm by 0.8 mm, contained within an off-white knitted polyester pouch retrieval system (see Figure 2).

Figure 2: CERVIDIL Components



4 CONTRAINDICATIONS

CERVIDIL is contraindicated in patients with:

- Known hypersensitivity to prostaglandins [see *Adverse Reactions (6.2)*]
- Evidence or clinical suspicion of fetal distress where delivery is not imminent
- Unexplained vaginal bleeding in the current pregnancy
- Evidence or clinical suspicion of marked cephalopelvic disproportion
- Conditions for which induction of labor is contraindicated
- Conditions for which oxytocic drugs are contraindicated
- Previous cesarean section or other uterine surgery expected to affect uterine integrity (such as myomectomy)
- Conditions under which prolonged contraction of the uterus may be detrimental to fetal safety
- Concurrent use with intravenous oxytocic agents [see *Warnings and Precautions (5.4)* and *Drug Interactions (7)*]

- Six or more previous term pregnancies

5 WARNINGS AND PRECAUTIONS

5.1 For Hospital Use Only

CERVIDIL should be administered in a hospital setting with an obstetrical care facility.

5.2 Disseminated Intravascular Coagulation

CERVIDIL should be used with caution in women at high risk of postpartum disseminated intravascular coagulation (DIC). Physiologic or pharmacologic induction of labor, including the use of CERVIDIL, is associated with an increased risk of DIC during the postpartum period. Women aged 30 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have an increased risk of DIC during the postpartum period. As soon as possible, assess for an evolving fibrinolysis in the immediate post-partum period. Therapy consisting of prompt removal of the source of procoagulant material, replacement of depleted clotting factors and, in some cases, anti-coagulation with heparin should be instituted promptly.

5.3 Amniotic Fluid Embolism Syndrome

The use of dinoprostone-containing products, including CERVIDIL, can result in inadvertent disruption and subsequent embolization of antigenic tissue causing the development of Amniotic Fluid Embolism Syndrome, a rare and often fatal obstetric condition.

Carefully monitor patients for clinical signs of Amniotic Fluid Embolism Syndrome including hypotension, hypoxemia and respiratory failure, DIC, coma or seizures and provide supportive care as needed.

5.4 Uterine Tachysystole and Uterine Hypersystole/Hypertonicity

The use of CERVIDIL may cause uterine tachysystole with or without fetal heart rate changes (see Table 1). While using CERVIDIL, carefully monitor uterine activity, fetal status and the progression of cervical dilatation and effacement. Remove CERVIDIL with any evidence of uterine tachysystole, uterine hypersystole/hypertonicity, fetal distress, or if labor commences. CERVIDIL is contraindicated when prolonged contraction of the uterus is detrimental to fetal safety or uterine integrity, such as previous cesarean section or major uterine surgery, because of the risk of uterine rupture and obstetrical complications (e.g., need for hysterectomy and the occurrence of fetal or neonatal death). Prostaglandins, including CERVIDIL, may potentiate the effect of oxytocin [see *Drug Interactions (7)*]. Remove CERVIDIL at least 30 minutes before administration of an oxytocic agent is initiated and continue to carefully monitor uterine activity. Remove CERVIDIL prior to amniotomy or following rupture of membranes because the higher vaginal pH that occurs with rupture of membranes may result in higher release rate of dinoprostone.

5.5 Glaucoma

Prostaglandins, including CERVIDIL, can lead to raised intraocular pressure and constriction of pupils. Consider non-prostaglandin cervical ripening procedures in

patients with Glaucoma.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Disseminated Intravascular Coagulation [see *Warnings and Precautions (5.2)*]
- Amniotic Fluid Embolism [see *Warnings and Precautions (5.3)*]
- Uterine Tachysystole and Uterine Hypersystole/Hypertonicity [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In placebo-controlled trials of 658 pregnant women (320 CERVIDIL-treated women and 338 placebo-treated women), the following treatment related adverse reactions (see Table 1) occurred at an incidence greater than 2% (and greater than that reported in the placebo group) in the CERVIDIL group [see *Clinical Studies (14)*].

Table 1. Common Adverse Reactions ($\geq 2\%$) in Pregnant Patients Near Term Gestation in Trial 1*, Trial 2*, and Trial 3†

	<u>Trials 1* and 2*</u>	
	CERVIDIL (N=320)	Placebo (N=338)
Uterine tachysystole with fetal distress	2.8%	0.3%
Uterine tachysystole without fetal distress	4.7%	0%
Fetal distress without uterine tachysystole -	3.8%	1.2%
	<u>Trial 3†</u>	
	CERVIDIL (N=102)	Placebo (N=104)
Uterine tachysystole with fetal distress	2.9%	0%
Uterine tachysystole - without fetal distress	2%	0%
Fetal distress without uterine tachysystole	2.9%	1%

* Trial 1 (101-103) and Trial 2 (101-003) evaluated the dinoprostone insert only, without the use of a retrieval system

† Trial 3 (101-801) evaluated the dinoprostone insert with the retrieval system.

Drug related fever, nausea, vomiting, diarrhea, and abdominal pain occurred in less than 1% of CERVIDIL-treated patients.

In Trial 3 (with the retrieval system) cases of tachysystole uterine hyperstimulation reversed within 2 to 13 minutes of removal of CERVIDIL. Tocolytics were required in one

of the five cases.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of CERVIDIL or other dinoprostone products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Disseminated Intravascular Coagulation

Cardiovascular disorders: Myocardial Infarction in women with a history of myocardial infarction

Immune system disorders: Hypersensitivity

Nervous system disorders: Headache

Pregnancy, puerperium and perinatal conditions: Amniotic fluid embolism

Reproductive system: reports of uterine rupture have been reported in association with use of CERVIDIL. Some required a hysterectomy and others resulted in subsequent fetal or neonatal death. Uterine hypertonus

Vascular disorders: Hypotension

7 DRUG INTERACTIONS

7.1 Oxytocic Agents

CERVIDIL is contraindicated in patients receiving intravenous oxytocic agents because CERVIDIL may augment the activity of oxytocic agents. A dosing interval of at least 30 minutes is recommended for the sequential use of an oxytocic agent following the removal of CERVIDIL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

CERVIDIL is indicated for the initiation and/or continuation of cervical ripening in pregnant women at or near term in whom there is a medical or obstetrical indication for the induction of labor. Fetal, neonatal, and maternal risks are discussed throughout the labeling. Limited available data with CERVIDIL use in pregnant women do not show a clear association with adverse developmental outcomes. Relevant animal reproduction data with dinoprostone is not available.

Data

Human Data

In a report of a 3-year pediatric follow-up study, there were no deleterious effects noted on physical examination or psychomotor evaluation of 51 infants born following maternal treatment with CERVIDIL.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

When CERVIDIL was removed for fetal distress, there was a return to normal rhythm and there were no neonatal sequelae. Remove CERVIDIL in the event of persistent tachysystole with or without fetal heart rate changes, and follow established institutional protocols in management of patients.

8.2 Lactation

Risk Summary

Concomitant administration of CERVIDIL is not indicated in breastfeeding women. There is no information on the effects of maternal CERVIDIL administration on the breastfed child. Insufficient information is available on the effects of maternal CERVIDIL administration on milk production.

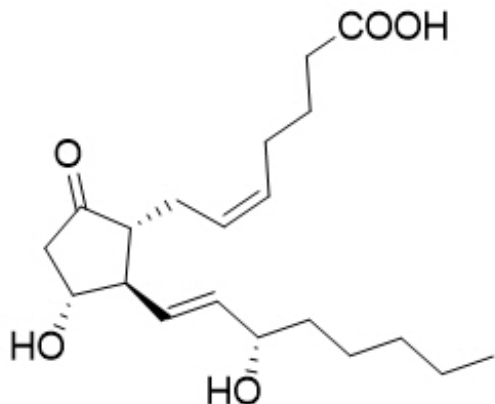
8.4 Pediatric Use

The safety and effectiveness of CERVIDIL have not been established in pregnant girls.

11 DESCRIPTION

CERVIDIL (dinoprostone) vaginal insert contains dinoprostone, a prostaglandin analog. Each vaginal insert contains 10 mg of dinoprostone in 241 mg of a cross-linked polyethylene oxide/urethane polymer (hydrogel polymer) that is semi-opaque, beige colored, flat, rectangular in shape with rounded corners and measuring 29 mm by 9.5 mm by 0.8 mm. The vaginal insert is contained within a pouch of an off-white knitted polyester yarn retrieval system. When placed in a moist environment, the yarn absorbs water, swells, and releases the enclosed dinoprostone. The knitted polyester retrieval system has a long tape-like end that is designed to aid retrieval of CERVIDIL at the end of the dosing interval or earlier if clinically indicated. The finished product is a controlled-release formulation that has been found to release dinoprostone *in vivo* at a rate of approximately 0.3 mg per hour.

The chemical name for dinoprostone (known as prostaglandin E₂ or PGE₂) is 11 α ,15S-dihydroxy-9-oxo-prosta-5Z,13E-dien-1-oic acid and the structural formula is represented below:



The molecular formula is $C_{20}H_{32}O_5$ and its molecular weight is 352.47. Dinoprostone occurs as a white to off-white crystalline powder. It has a melting point within the range of 65° to 69°C. Dinoprostone is soluble in ethanol and in 25% ethanol in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dinoprostone is found in low concentrations in most tissues of the body and functions as a local hormone. In pregnancy, dinoprostone is secreted continuously by the fetal membranes and placenta and plays an important role in the final events leading to the initiation of labor including cervical ripening. Dinoprostone stimulates the production of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), which sensitizes the myometrium to endogenous or exogenously administered oxytocin. Available evidence indicates that dinoprostone, in the concentrations found during the early part of labor, plays an important role in cervical ripening without affecting uterine contractions.

In most patients, local effects of CERVIDIL on the cervix include changes in the tissue consistency, dilatation and effacement. Some women experience systemic effects, including uterine tachysystole, and uterine hypersystole/hypertonicity, as a result dinoprostone or $PGF_{2\alpha}$ mediated sensitization of the myometrium to oxytocin [see *Warnings and Precautions* (5.4)].

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with CERVIDIL.

12.3 Pharmacokinetics

The delivery rate of dinoprostone from CERVIDIL *in vivo* is approximately 0.3 mg/per hour over a period of 12 hours. Dinoprostone is metabolized in the tissues of synthesis with the half-life estimated to be 2.5 to 5 minutes. The rate limiting step for inactivation is regulated by the enzyme 15-hydroxyprostaglandin dehydrogenase (PGDH). Any dinoprostone that escapes local inactivation is cleared to the extent of 95% on the first pass through the pulmonary circulation.

No correlation could be established between the release of dinoprostone from CERVIDIL and plasma concentrations of metabolite of dinoprostone (PGE_m). The relative contributions of endogenously and exogenously released dinoprostone to the plasma levels of the metabolite PGE_m is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity and fertility studies have not been conducted with dinoprostone. No evidence of mutagenicity has been observed with dinoprostone in the Unscheduled DNA Synthesis Assay, the Micronucleus Test, or the bacteria reverse mutation (Ames) test.

14 CLINICAL STUDIES

The effectiveness and safety of CERVIDIL for the induction of cervical ripening was evaluated in 658 pregnant women (320 CERVIDIL-treated women and 338 placebo-treated women) at or near term in three randomized, double-blind, placebo-controlled trials (Trials 1, 2, and 3). Efficacy outcomes included percentage with treatment success (defined as vaginal delivery within 12 hours, Bishop Score ≥ 6 in the 12-hour observation period, or ≥ 3 increase in the Bishop score in the 12-hour observation period), time to delivery, and time to onset of labor. Table 2 presents efficacy outcomes from Trials 1, 2, and 3.

Table 2: Efficacy Outcomes in Pregnant Women in Trials 1*, 2,* and 3† for CERVIDIL Ripening, Intent-to-Treat Population

	Primipara/Nullipara		Multipara		
Study #	CERVIDIL	Placebo	CERVIDIL	Placebo	P-Value
Treatment Success‡					
Trial 1 (N=81)	65% (n=26)	28% (n=32)	87% (n=16)	29% (n=7)	<0.001
Trial 2 (N=371)	68% (n=111)	24% (n=123)	77% (n=65)	24% (n=72)	<0.001
Trial 3 (N=206)	72% (n=60)	48% (n=63)	55% (n=42)	41% (n=41)	0.003
Median Time to Delivery (hours)					
Trial 1 (N=81)	25.7 (n=26)	34.5 (n=32)	12.3 (n=16)	24.6 (n=7)	0.001
Trial 3 (N=206)	25.5 (n=60)	37.2 (n=63)	20.8 (n=42)	27.4 (n=41)	<0.001
Median Time to Onset of Labor (hours)					
Trial 1 (N=81)	12 (n=26)	19.2 (n=32)	6.9 (n=16)	18.3 (n=7)	<0.001

* Trial 1 and Trial 2 evaluated the dinoprostone insert only, without the use of a retrieval system.

† Trial 3 evaluated the dinoprostone insert with the retrieval system

‡ Treatment success was defined as vaginal delivery within 12 hours, Bishop score ≥ 6 in the 12-hour observation period, or ≥ 3 increase in the Bishop score in the 12-hour observation period.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

CERVIDIL vaginal insert contains 10 mg dinoprostone in a hydrogel polymer (NDC 55566-2800-1). The vaginal insert is beige-colored, semi-opaque, thin, flat, and rectangular in shape with rounded corners, measuring 29 mm by 9.5 mm by 0.8 mm, and is contained within an off-white knitted polyester pouch retrieval system.

CERVIDIL is enclosed in an aluminum/polyethylene pack.

Storage and Handling

Store in a freezer between -20°C and -10°C (-4°F and 14°F). CERVIDIL, enclosed in its aluminum/polyethylene pack, is stable when stored in a freezer for a period of three

years. Vaginal inserts exposed to high humidity will absorb moisture from the air and thereby alter the release characteristics of dinoprostone.

17 PATIENT COUNSELING INFORMATION

Administration

Advise the woman to remain in the recumbent position for 2 hours following CERVIDIL insertion and to inform her health care provider immediately if CERVIDIL does not remain in place *[see Dosage and Administration (2.2)]*.

Disseminated Intravascular Coagulation

Inform women that the use of CERVIDIL is associated with an increased risk of disseminated intravascular coagulation (DIC) during the postpartum period *[see Warnings and Precautions (5.2)]*.

Amniotic Fluid Embolism Syndrome

Inform women that the use of CERVIDIL can result in inadvertent disruption and subsequent embolization of antigenic tissue causing the development of Amniotic Fluid Embolism Syndrome, a rare and often fatal obstetric condition *[see Warnings and Precautions (5.3)]*.

Frequent or Prolonged Uterine Contractions

Inform women that the use of CERVIDIL may cause frequent or prolonged contractions *[see Warnings and Precautions (5.4)]*. This might result in disruption of blood flow through the placenta and to the fetus.

Glaucoma

Inform women that CERVIDIL can lead to raised intraocular pressure and constriction of pupils *[see Warnings and Precautions (5.5)]*.

Manufactured for:
Ferring Pharmaceuticals, Inc.
Parsippany, NJ 07054

PRINCIPAL DISPLAY PANEL - 10 mg Pouch Carton

NDC 55566-2800-1

Cervidil®
DINOPROSTONE 10mg
VAGINAL INSERT

Contains: One Cervidil® Vaginal Insert containing
10 mg Dinoprostone in 241 mg hydrogel polymer
(cross-linked polyethylene oxide/urethane)
with polyester retrieval system.

Store in a freezer:
between -20°C and -10°C (-4°F and 14°F)

FERRING

NDC 55566-2800-1



Contains: One Cervidil® Vaginal Insert containing 10 mg Dinoprostone in 241 mg hydrogel polymer (cross-linked polyethylene oxide/urethane) with polyester retrieval system.

**Store in a freezer:
between -20°C and -10°C (-4°F and 14°F)**



CERVIDIL

dinoprostone insert

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:55566-2800
Route of Administration	VAGINAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DINOPROSTONE (UNII: K7Q1JQR04M) (DINOPROSTONE - UNII:K7Q1JQR04M)	DINOPROSTONE	10 mg in 241 mg

Inactive Ingredients

Ingredient Name	Strength
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	

Product Characteristics

Color	white	Score	
Shape	RECTANGLE	Size	
Flavor		Imprint Code	
Contains			

Packaging

			Marketing Start	Marketing End
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#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55566-2800-1	1 in 1 CARTON	03/30/1995	
1	NDC:55566-2800-0	10 mg in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020411	03/30/1995	

Labeler - Ferring Pharmaceuticals Inc. (103722955)

Establishment			
Name	Address	ID/FEI	Business Operations
Ferring Controlled Therapeutics Ltd		298229634	manufacture(55566-2800) , pack(55566-2800)

Establishment			
Name	Address	ID/FEI	Business Operations
EUROAPI Hungary Ltd.		402388457	analysis(55566-2800) , api manufacture(55566-2800)

Establishment			
Name	Address	ID/FEI	Business Operations
Kyowa Pharma Chemical Co., Ltd.		690852371	api manufacture(55566-2800)