

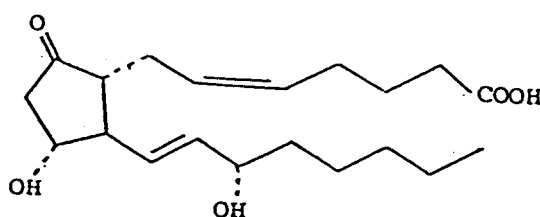
# PRODUCT INFORMATION

## PROSTIN<sup>®</sup> E<sub>2</sub> Vaginal Gel (1 mg and 2 mg dinoprostone vaginal gel)

### DESCRIPTION

PROSTIN E<sub>2</sub> Vaginal Gel is a translucent, glycerol triacetate-based, thixotropic gel formulation containing either 1 or 2 mg dinoprostone, as the active ingredient in each unit dose of 3 grams (2.5 mL).

Structural formula of dinoprostone:



Chemical name:

(5z,11- $\alpha$ ,13E,15s)-11,15-dihydroxy-9-oxo-prosta-5, 13-dien-1-oic acid.

Molecular formula: C<sub>20</sub>H<sub>32</sub>O<sub>5</sub>

Molecular weight: 352.5.

Dinoprostone is a white crystalline powder. It has a melting point range of 64° to 71°C. Dinoprostone is readily soluble in the glycerol triacetate component of the gel formulation. It is also soluble in ethanol and in 25% ethanol water. Solubility in water is limited to 130 mg/100 mL.

### CLINICAL PHARMACOLOGY

The major clinical application of PROSTIN E<sub>2</sub> Vaginal Gel relates to the ability of dinoprostone to produce cervical ripening and to stimulate myometrial contractions. These properties led to the development of this formulation for use in inducing labour in term or near term pregnant women.

Dinoprostone appears to exert its major action on the cervix and reproduces the action of the naturally occurring prostaglandins in promoting the process of softening and effacement known as "ripening". This process appears to be due to a combination of reduced collagen

concentration and dissociation of collagen fibrils together with alterations in glycosaminoglycan composition and hydration.

These changes facilitate cervical dilatation in the face of subsequent prostaglandin mediated uterine contractions.

In both laboratory animals and man, large doses of dinoprostone can lower blood pressure, probably as a consequence of its effect on smooth muscle of the vascular system. Transient elevations in body temperature have been observed with doses used for pregnancy termination.

### **Pharmacokinetics**

Dinoprostone is established as a successful agent for cervical ripening and induction of labour. Dinoprostone initiates labour by a process which may be more akin to spontaneous labour than that produced by forewater amniotomy followed by oxytocin infusion. Local application of dinoprostone (endocervical and vaginal) has proved to be clinically superior to intravenous administration, avoiding gastrointestinal side effects.

Distribution: Using equilibrium dialysis, studies indicate that dinoprostone is approximately 73% bound to human plasma albumin.

Metabolism: Dinoprostone is rapidly metabolised in the lungs, kidneys and liver. Approximately 90% of dinoprostone is metabolised in the first pass. In man three metabolites of dinoprostone have been identified in plasma:

- A. 13,14-dihydro-15-keto GE<sub>2</sub> (the primary metabolite)
- B. 11 alpha-hydroxy-9,15-diketoprost-5-enoic acid
- C. 11 alpha-hydroxy-9,15-dioxyprost-5-13-dienoic acid

Excretion: Dinoprostone is eliminated from the circulation very rapidly. Studies indicate that the half life of dinoprostone is less than one minute.

The plasma concentration of dinoprostone and its metabolites is low after intravaginally administered PROSTIN E2 Vaginal Gel. The plasma half-life for dinoprostone is less than 1 minute and for its primary metabolite less than 10 minutes. Animal studies have shown that this metabolite (15-keto-13, 14 dihydro-PGE<sub>2</sub>) is about half as active as the mother substance. Dinoprostone is metabolised in the lung and is excreted via the urine.

## **INDICATIONS**

Induction of labour in term or near-term pregnant women who have favourable induction features; and who have singleton pregnancy with a vertex presentation.

## **CONTRAINDICATIONS**

PROSTIN E2 Vaginal Gel should not be used in patients known to be hypersensitive to dinoprostone or any other constituent of the gel (glycerol triacetate or silica - colloidal anhydrous).

PROSTIN E2 Vaginal Gel should not be used in patients with any of the following:

1. Grand multiparity (five or more previous deliveries).
2. Cases in which the presenting part is above the pelvic inlet.
3. History of previous uterine surgery.
4. Cephalopelvic disproportion.
5. Abnormal cardiotocography or suspected fetal compromise.
6. Malpresentation.
7. Unexplained vaginal discharge and/or abnormal uterine bleeding during the current pregnancy.
8. Cases where vaginal delivery is not indicated such as vasa praevia or active herpes genitalis.
9. Multiple gestation.
10. Fetal heart rate pattern suggests incipient fetal compromise.
11. Obstetric conditions where either maternal or fetal benefit/risk ratio favours surgical intervention.

## **PRECAUTIONS**

**PROSTIN E2 Vaginal Gel should not be used simultaneously with other oxytocics, however they may be used in sequence (see PRECAUTIONS).**

PROSTIN E2 Vaginal Gel is an intravaginal product. It is not to be used intra-cervically. The intracervical placement of dinoprostone gel may result in inadvertent disruption and subsequent embolization of antigenic tissue. This may cause, in rare circumstances, the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

PROSTIN E2 Vaginal Gel for labour induction should be used with caution in patients with compromised **cardiovascular, hepatic or renal function** and in patients with **asthma, epilepsy, glaucoma or raised intraocular pressure, or ruptured chorioamniotic membranes**.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labour induction (see ADVERSE REACTIONS). Therefore, in these women, use of PROSTIN E2 Vaginal Gel should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

Caution is advised when PROSTIN E2 Vaginal Gel is applied in the presence of ruptured chorioamniotic membranes, as there is a theoretical risk of increased absorption (due to an increased pH) and because of this, there is a risk of increased uterine hypertonicity.

PROSTIN E2 Vaginal Gel should only be used under the supervision of qualified medical personnel in obstetric units with facilities for fetal and maternal monitoring and operative delivery.

It is recommended that during induction of labour with PROSTIN E2 Vaginal Gel that continuous monitoring of uterine activity and fetal heart rate be employed.

As with other oxytocic agents, the possibility of uterine rupture should be considered in the presence of excessive uterine activity or unusual uterine pain.

PROSTIN E2 Vaginal Gel should be used with caution in patients with cervical (Bishop) scores of 8 or more.

### **Use with other Oxytocic Agents**

The response to oxytocin may be accentuated in the presence of exogenous prostaglandin therapy. PROSTIN E2 Vaginal Gel should not be used simultaneously with other oxytocics, and when used sequentially, uterine activity should be carefully monitored.

### **Use in Pregnancy (Category C)**

Because PROSTIN E2 Vaginal Gel is an oxytocic agent, its appropriate use during pregnancy is for the induction of labour in the term or near term patient.

Prostaglandin E2 produced an increase in skeletal anomalies in rats and rabbits and has been shown to be embryotoxic in rats and rabbits.

Any dose that produces sustained increased uterine tone could put the embryo or fetus at risk.

### **Use in Lactation**

Prostaglandins are excreted in breast milk at very low concentrations.

### **Interactions with Other Medicines**

The response to oxytocin may be accentuated in the presence of exogenous prostaglandin therapy. Concurrent use with other oxytocic agents is not recommended.

## **ADVERSE EFFECTS**

The following medical events have been seen in patients treated with PROSTIN E2 Vaginal Gel for labour induction:

Altered fetal heart rate patterns diagnosed as fetal distress (10.3%). Still births have been reported.

## Uterine hypercontractility and hypertonus:

The principal expressions of an exaggerated response to PROSTIN E2 Vaginal Gel are either myometrial hypercontractility or hypertonus. Management of an exaggerated myometrial response should include digital removal of the gel and swabbing of the vagina. The dilation and effacement of the cervix and the fetal heart rate should be noted.

The patient should be placed in a lateral semirecumbent position and oxygen administered if necessary.

Consideration should be given to the use of a uterine relaxant such as a beta sympathomimetic if necessary.

## Disseminated intravascular coagulation

In post-marketing surveillance, an increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour was induced by pharmacological means, including dinoprostone (see PRECAUTIONS). The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labours).

Other medical events which may be observed are:

- Post partum haemorrhage
- Uterine rupture
- Post operative infection
- Vaginal irritation
- Warm feeling in vagina
- Amniotic fluid embolism
- Nausea, vomiting, diarrhoea and fever
- Back pain
- Hypersensitivity reactions (e.g., \*anaphylactic reaction, \*anaphylactic shock and \*anaphylactoid reaction)

Medical events related to systemic prostaglandin use that have been reported with oral or intravenous administration, may be observed although the absorption of the PROSTIN E2 Vaginal Gel systemically appears to be minimal:

These include:

- Pyrexia
- Hypertension
- Cardiac arrest
- Bronchoconstriction
- Asthma
- Headache/epigastric and chest pain
- Allergic reactions
- Vasovagal symptoms (shivering, headache, dizziness)
- Blurring of vision
- Facial flush
- Abruptio placenta
- Rapid cervical dilation,

## DOSAGE AND ADMINISTRATION

For labour induction at or near term, in women with favourable induction features with singleton pregnancy and vertex presentation, the initial dose is 1 mg of PROSTIN E2 Vaginal Gel.

1. Remove the syringe containing the gel from refrigeration at least 30 minutes prior to use and allow to warm to room temperature.
2. The gel should be inserted high into the posterior fornix of the vagina, avoiding administration into the cervical canal.
3. The patient should be instructed to remain recumbent for at least 30 minutes.

Each syringe containing a prescribed amount of PROSTIN E2 Vaginal Gel (1 mg or 2 mg) is for single use only. Discard after initial use.

A further dose of either 1 or 2 mg of PROSTIN E2 Vaginal Gel may be given after 6 hours on the basis of clinical assessment of response on the proviso that the maximum dose of PROSTIN E2 Vaginal Gel does not exceed 3 mg (or 60 µg/kg for a 50 kg woman) over a 6 hour period.

Use of PROSTIN E2 Vaginal Gel in situations other than that indicated is inappropriate and is not recommended.

## METHOD OF ASSEMBLY

### STEP ONE:

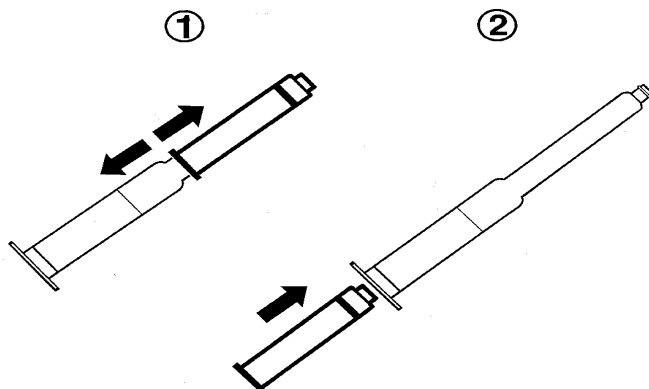
Remove protective end cap (to serve as plunger rod).

### STEP TWO:

Insert protective end cap into the syringe.

### STEP THREE:

Administer syringe content.



## **OVERDOSAGE**

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. Because of the transient nature of PGE<sub>2</sub>-induced myometrial hyperstimulation, nonspecific, conservative management was found to be effective in the vast majority of the cases; i.e., maternal position change and administration of oxygen to the mother. Where there is evidence of fetal distress or uterine hypertonus, then prompt delivery is indicated. B-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PROSTIN E2 Vaginal gel for cervical ripening.

Contact the Poisons Information Centre for advice on the management of an overdose.

## **PRESENTATION**

PROSTIN E2 Vaginal Gel is available in single packs of 1 or 2 mg. The contents of one syringe are to be used for a single patient. Discard after use.

## **STORAGE CONDITIONS**

PROSTIN E2 Vaginal Gel may be stored at 2° to 8°C, under continuous refrigeration for up to 24 months. Before use, allow the gel to stand at room temperature for 30 minutes.

## **NAME AND ADDRESS OF THE SPONSOR**

Pfizer Australia Pty Ltd  
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38-42 Wharf Road  
West Ryde NSW 2114  
Australia

## **DATE OF APPROVAL**

Approved by TGA: 3 May 2005

Date of most recent amendment: 12 January 2012

\*Please note changes to Product Information.

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