

AUSTRALIAN PRODUCT INFORMATION - PROSTIN[®] E₂ VAGINAL GEL (DINOPROSTONE)

1. NAME OF THE MEDICINE

Dinoprostone.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROSTIN E2 Vaginal Gel contains either 1 mg or 2 mg dinoprostone, as the active ingredient in each unit dose of 3 grams (2.5 mL).

3. PHARMACEUTICAL FORM

Vaginal Gel.

PROSTIN E2 Vaginal Gel is a translucent triacetin-based, thixotropic gel formulation.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of 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:

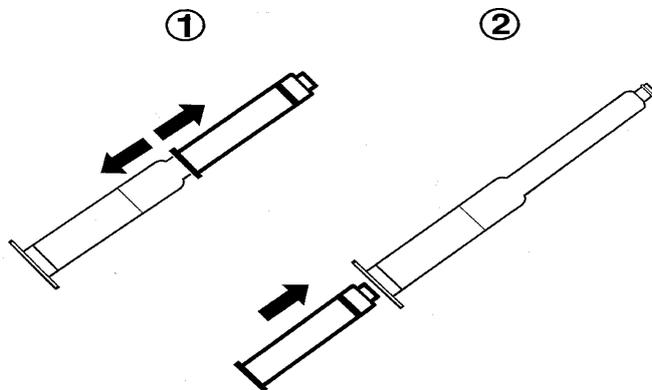
Remove protective end cap (to serve as plunger rod).

STEP TWO:

Insert protective end cap into the syringe.

STEP THREE:

Administer syringe content.



4.3 Contraindications

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

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

Grand multiparity (five or more previous deliveries).

Cases in which the presenting part is above the pelvic inlet.

History of previous uterine surgery.

Cephalopelvic disproportion.

Abnormal cardiotocography or suspected fetal compromise.

Malpresentation.

Unexplained vaginal discharge and/or abnormal uterine bleeding during the current pregnancy.

Cases where vaginal delivery is not indicated such as vasa praevia or active herpes genitalis.

Multiple gestation.

Fetal heart rate pattern suggests incipient fetal compromise.

Obstetric conditions where either maternal or fetal benefit/risk ratio favours surgical intervention.

4.4 Special warnings and precautions for use

PROSTIN E2 Vaginal Gel should not be used simultaneously with other oxytocics, however they may be used in sequence (see Section 4.4 Special warnings and precautions for use, Use with other Oxytocic Agents).

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 Section 4.8 Adverse effects (undesirable effects)). 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 the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

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.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable 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 Section 4.4 Special warnings and precautions for use). 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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. Because of the transient nature of PGE₂-induced myometrial hyperstimulation, nonspecific, conservative management was found to be effective in the vast majority of the cases; i.e., maternal position change and administration of oxygen to the mother. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The major clinical application of PROSTIN E2 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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

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 GE₂ (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-PGE₂) is about half as active as the mother substance. Dinoprostone is metabolised in the lung and is excreted via the urine.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Triacetin

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

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.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal

Discard after use.

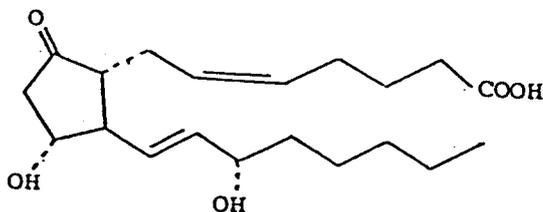
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Dinoprostone is a white crystalline powder. It has a melting point range of 64° to 71°C. Dinoprostone is readily soluble in the triacetin 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.

Chemical structure

Structural formula of dinoprostone:



Chemical name:

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

Molecular formula: $C_{20}H_{32}O_5$

Molecular weight: 352.5.

CAS number

363-24-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

27 August 1991

10. DATE OF REVISION

2 March 2020

Summary Table of Changes

| Section changed | Summary of new information |
|-----------------|--|
| Throughout | Reformatting of PI including minor editorial changes to align with the revised format. |
| 8 | Updated Sponsor address. |

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