1 NAME OF THE MEDICINAL PRODUCT

Prostin® E2 Vaginal Gel 1 mg

Prostin® E2 Vaginal Gel 2 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 g gel (2.5 ml) contains 1 mg dinoprostone.

Each 3 g gel (2.5 ml) contains 2 mg dinoprostone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel for intravaginal application.

Semi-translucent viscous gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

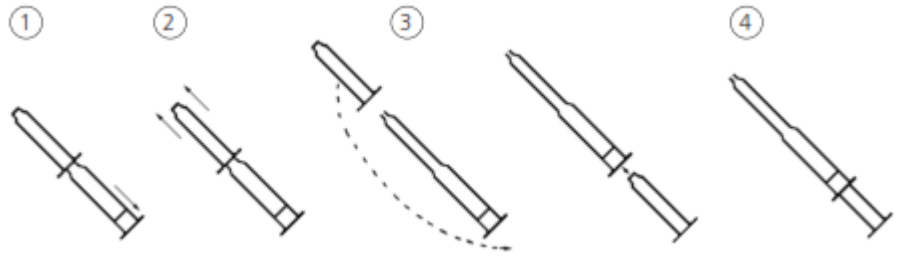
Prostin E2 Vaginal Gel is indicated for labor induction in term and near term pregnant women who have favorable induction features and who have singleton pregnancy with a vertex presentation.

4.2 Posology and method of administration

Usage is restricted to qualified health care professionals and to hospitals and clinics with specialised obstetric units with facilities for continuous monitoring.

The recommended dose should not be exceeded, and the dosing interval should not be shortened as this increases the risk of uterine hyperstimulation, uterine rupture, uterine haemorrhage, foetal and neonatal death.
For labor induction at or near term, the initial dose of 1 mg of Prostin E2 Vaginal Gel should be administered by gentle expulsion of the entire content of the syringe into the posterior fornix of the vaginal canal. The patient should remain in supine position for at least 30 minutes. After 6 hours, a second dose of either 1 or 2 mg of Prostin E2 Vaginal Gel may be administered if necessary:
- 2 mg in case of absence of response to initial dose;
- 1 mg to augment an already present response to the initial dose.

SYRINGE ASSEMBLY INSTRUCTIONS:



1. Remove peel-off seal.
2. Remove protective end cap (to serve as plunger rod).
3. Insert protective end cap into the syringe.
4. Administer syringe content.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1. Prostin E2 Vaginal Gel should not be used where the patient is sensitive to prostaglandins or other constituents of the gel.

Prostin E2 Vaginal Gel is not recommended in the following circumstances:

- For patients in whom oxytocic drugs are generally contra-indicated or where prolonged contractions of the uterus are considered inappropriate such as:
  - Cases with a history of Caesarean section or major uterine surgery.
  - Cases where there is cephalopelvic disproportion.
  - Cases in which foetal malpresentation is present.
  - Cases where there is clinical suspicion or definite evidence of pre-existing foetal distress.
  - Cases in which there is a history of difficult labour and/or traumatic delivery.
- In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been instituted.
- In patients where there is clinical suspicion or definite evidence of placenta praevia or unexplained vaginal bleeding during this pregnancy.
- Patients with active cardiac, pulmonary, renal or hepatic disease.

4.4 Special warnings and precautions for use

This product is only available to hospitals and clinics with specialised obstetric units and should only be used where 24-hour resident medical cover is provided.

Use the total contents of the syringe for one patient only. Discard after use. Use caution in handling the product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

As with any oxytocic agent, the risk of uterine rupture should be considered. Concomitant medication, maternal and foetal status should be taken into consideration in order to minimise the risk of uterine hyperstimulation, uterine rupture, uterine haemorrhage, foetal and neonatal death. Careful and regular monitoring of uterine activity and foetal heart rate should be

conducted during use of dinoprostone. Patients who develop uterine hypertonus or hypercontractility, or in whom unusual foetal heart rate patterns develop, should be managed in a manner that addresses the welfare of the foetus and mother.

Prostin E2 Vaginal Gel and Prostin E2 Vaginal Tablets are not bioequivalent.

Caution should be exercised in the administration of Prostin E2 Vaginal Gel for the induction of labour in patients with:

- asthma or a history of asthma
- epilepsy or a history of epilepsy
- glaucoma or raised intra-ocular pressure
- compromised cardiovascular, hepatic, or renal function
- hypertension
- ruptured chorioamniotic membranes.

Dinoprostone should be used with caution in patients with multiple pregnancy.

In labour induction, cephalopelvic relationships should be carefully evaluated before use of Prostin E2 Vaginal Gel. During use, uterine activity, foetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus, sustained uterine contractions, or foetal distress.

In cases where there is a known history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the foetus (where applicable) should be continuously monitored throughout labour. The possibility of uterine rupture should be borne in mind where high-tone uterine contractions are sustained.

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 received prostaglandin E_1 during prolonged treatment. There is no evidence that short-term administration of prostaglandin E_2 can cause similar bone effects.

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). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

4.5 Interaction with other medicinal products and other forms of interaction

The response to oxytocin may be accentuated in the presence of exogenous prostaglandin therapy. Concurrent use with other oxytocic agents is not recommended A dosing interval of at least 6 hours is recommended in case of oxytocin use is considered necessary following dinoprostone administration. If used in sequence, the patient's uterine activity should be carefully monitored.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

Prostin E2 Vaginal Gel is only used during pregnancy, to induce labour.

Breast-feeding
Prostaglandins are excreted in breast milk. This is not expected to be a hazard given the circumstances in which the product is used.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1 000 to <1/100); Rare (≥ 1/10 000 to <1/1 000); Very Rare (< 1/10 000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Adverse Reactions

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1 000 to <1/100	Rare ≥1/10 000 to <1/1 000	Very Rare <1/10 000	Frequency Not Known (Cannot Be Estimated From Available Data)
Blood and lymphatic system disorders				Disseminated intravascular coagulation*		
Immune system disorders						Hypersensitivity, Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction
Cardiac disorders						Cardiac arrest
Vascular disorders						Hypertension**
Respiratory, thoracic and mediastinal disorders						Asthma**, Bronchospasm**
Gastrointestinal disorders	Vomiting	Nausea				Diarrhoea
Skin and subcutaneous tissue disorders						Rash
Musculoskeletal and connective tissue disorders		Back pain				

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1 000 to <1/100	Rare ≥1/10 000 to <1/1 000	Very Rare <1/10 000	Frequency Not Known (Cannot Be Estimated From Available Data)
Pregnancy, Puerperium and Perinatal conditions		Uterine hypertonus, Foetal distress syndrome, Uterine contractions abnormal				Uterine rupture, Premature separation of placenta, Anaphylactoid syndrome of pregnancy**, Rapid cervical dilatation, Neonatal distress, Death neonatal††, Stillbirth†, Foetal death
Reproductive system and breast disorders		Vulvovaginal burning sensation				Irritation, Pain
General disorders and administration site conditions		Pyrexia				
Investigations	Foetal heart rate abnormal					Apgar score low

* Reported during post marketing surveillance
** Maternal adverse events that have been reported only with use of the vaginal tablets.
† Foetal adverse events that have been reported with use of the cervical gel, intravaginal gel and vaginal tablets.
†† Foetal adverse event has only been reported with vaginal tablets.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form **https://sideeffects.health.gov.il/**

4.9 Overdose

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. During use, uterine activity, foetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus, sustained uterine contractions, or foetal distress. Because of the transient nature of prostaglandin E_2 (PGE2)-induced myometrial hyperstimulation, non-specific, conservative management was found to be effective in the vast majority of cases: i.e. maternal position change and administration of oxygen to the mother. If conservative management is not effective, ß-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PGE2 for cervical ripening, in appropriate patients.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prostaglandins, ATC-code: G02AD02

Dinoprostone is a prostaglandin of the E series which induces myometrial contractions and promotes cervical ripening.

5.2 Pharmacokinetic properties

When given vaginally, PGE_2 is rapidly absorbed. Plasma levels of 15-keto PGE_2 equivalents peak at 1.5 hours after administration of a 5 mg dose. *In vitro* work indicates that PGE_2 is 73% bound to human plasma albumin. It is rapidly metabolised in the lungs, kidneys, spleen and liver, with a single pass of the circulatory system converting 90% of an injected PGE_2 dose to metabolites.

5.3 Preclinical safety data

There are no preclinical data of relevance which are additional to those already included in other sections of this Prescribing Information leaflet.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica and glycerol triacetate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator at 2-8°C.

6.5 Nature and contents of container

Low density polyethylene (LDPE) syringe containing 3 g gel (2.5 ml).

6.6 Special precautions for disposal and other handling

Use the total contents of the syringe for one patient only. Discard after use. Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

7 LICENSE HOLDER

Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya, 4672509.

8 LICENSE NUMBER(s)

Prostin E2 Vaginal Gel 1 mg : 056-32-26453-00

Prostin E2 Vaginal Gel 2 mg : 056-33-26455-00

Revised in 03/2026