SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prostin E2 2 mg Vaginal Gel.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Vaginal gel.

Translucent, thixotropic gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction of labour in the absence of foetal and maternal contraindications.

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.

Adults: In primigravida patients with unfavourable induction features (Bishop score of 4 or less), an initial dose of 2 mg should be administered vaginally. In other patients an initial dose of 1 mg should be administered vaginally.

In both groups of patients, a second dose of 1 mg or 2 mg may be administered after 6 hours as follows:

1 mg should be used where uterine activity is insufficient for satisfactory progress of labour.

2 mg may be used where response to the initial dose has been minimal.

Maximum dose 4 mg in unfavourable primigravida patients or 3 mg in other patients (see section 4.4).

The gel should be inserted high into the posterior fornix avoiding administration into the cervical canal. The patient should be instructed to remain recumbent for at least 30 minutes.

After insertion of the gel the patient should be under observation using continual external cardiotocography to monitor foetal heart rate and uterine activity.

Elderly: Not applicable.

Paediatric population: Not applicable.

4.3 Contraindications

Hypersensitivity to dinoprostone, other prostaglandins or to any of the excipients listed in section 6.1.

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

1. For patients in whom oxytocic drugs are generally contraindicated 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
- Multiple gestation
- Engagement of the head has not taken place
- Obstetric conditions where either maternal or foetal benefit / risk ratio favours surgical intervention.

2. In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been instituted.

3. In patients where there is clinical suspicion or definite evidence of placenta praevia or unexplained vaginal discharge and /or abnormal bleeding during this pregnancy.

4. 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. Continuous electronic 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:

(i) asthma or a history of asthma
(ii) epilepsy or a history of epilepsy
(iii) glaucoma or raised intra-ocular pressure
(iv) compromised cardiovascular, hepatic, or renal function
(v) hypertension
(vi) 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. 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.

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 the 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 those women the use of Prostin E2 Vaginal Gel should be done with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

The Clinician should be alert that the intracervical placement of dinoprostone gel may result in advertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 applicable.

4.8 Undesirable effects

The most commonly reported events are vomiting, nausea and diarrhoea. Certain rare events that should be especially noted are: hypersensitivity reactions (e.g. anaphylactic reaction, anaphylactic shock, anaphylactoid reaction); uterine rupture and cardiac arrest. Other adverse events reported with use of dinoprostone are:

- Pulmonary / amniotic fluid embolism
- Abruptio placenta
- Uterine hypercontractility or hypertonus
- Foetal distress / altered foetal heart rate (FHR)
- Hypertension - systemic (maternal)
- Bronchospasm / asthma
- Rapid cervical dilation
- Fever
- Backache
- Rash
- Vaginal symptoms - warmth, irritation, pain
- Neonatal distress / low Apgar scores in the new-born
- Coma.
- Foetal death, stillbirth, neonatal death* (Frequency not known- cannot be estimated from the available data).

*Foetal death, stillbirth, and neonatal death have been reported after application of dinoprostone, especially following the occurrence of serious events such as uterine rupture (see sections 4.2, 4.3 and 4.4).

An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour was induced by pharmacological means, either with dinoprostone or oxytocin (see section 4.4). The frequency of this adverse event, however, appears to be rare (< 1 per 1,000 labours).

Reporting of 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Uterine hypertonus or unduly severe uterine contractions have rarely been encountered, but might be anticipated to result from overdosage. Where there is evidence of foetal distress or uterine hypertonus, then prompt delivery is indicated. Treatment of overdosage must be, at this time, symptomatic, since clinical studies with prostaglandin antagonists have not progressed to the point where recommendations may be made.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dinoprostone is a prostaglandin of the E series with actions on smooth muscle; the endogenous substance is termed prostaglandin E2 (PGE_2). It induces contraction of uterine muscle at any

stage of pregnancy and is reported to act predominantly as a vasodilator on blood vessels and as a bronchodilator on bronchial muscle. It is postulated that vaginal absorption of PGE_2 stimulates endogenous PGE_2 and $PGF_{2\alpha}$ production, similar to that which is seen in spontaneous labour.

5.2 Pharmacokinetic properties

General characteristics of active substance

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.

There has been found to be inter-patient variability regarding systemic absorption of PGE_2. This can be attributed to different conditions of the vaginal mucosa between patients.

Characteristics in patients

No special characteristics (see section 4.4 for further information).

5.3 Preclinical safety data

In mice and rats, the oral LD_{50} values were >500 mg/kg and 141-513 mg/kg respectively.

Three month oral administration to rats resulted in significantly heavier stomach weights for treated compared with untreated rats, which effect was reversible on treatment cessation. Treated rats had a dose related acanthotic squamous glandular junction and thickened glandular gastric mucosal epithelium. No significant alterations were recognized in routine evaluation of the sternebrae and the femur.

A fourteen day oral toxicity study in dogs showed a maximum tolerated dose of 6-20 mg/kg/day. All treated dogs had microscopic evidence of increased fundic and pyloric mucus. The fundic and pyloric mucosa were thickened, having a cobblestone appearance and had an increased gastric mucus in both 20 mg/kg/day treated dogs and the 60 mg/kg/day male dog. These were the only gross and microscopic drug related changes observed.

Satisfactory results were obtained in intravenous and intramuscular tolerability tests performed in dog and monkey.

Teratogenic effects were observed in rats injected subcutaneously with 0.5 mg/animal. No teratogenic effects were seen in the rabbit at dosage levels of up to 1.5 mg/kg/day.

No evidence of mutagenicity was obtained using the Ames Assay, the DNA Damage/Alkaline Elution Assay and the micronucleus test.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triacetin
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

6.5 Nature and contents of container

The gel is contained in a singly packed disposable polyethylene syringe containing 3g of thixotropic gel in 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. MARKETING AUTHORIZATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
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8. MARKETING AUTHORISATION NUMBER

PA 822/178/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th March 1987
Date of last renewal: 13th March 2007

10. DATE OF REVISION OF THE TEXT

10/2024

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