PROSTIN E2®
(Dinoprostone)

1. NAME OF THE MEDICINAL PRODUCT

PROSTIN E2®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: dinoprostone as the naturally occurring prostaglandin E2 (PGE2).
Vaginal tablets containing 3 mg dinoprostone.

3. PHARMACEUTICAL FORM

Vaginal Tablets

4. CLINICAL PARTICULAR

4.1. THERAPEUTIC INDICATIONS

PROSTIN E2® is indicated for the induction of labor in pregnant women at or near term.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

The initial dose is 1 tablet (3 mg) of Prostin E2® inserted high into the posterior fornix. A second tablet may be inserted after 6-8 hours if labor has not been established. The maximum or total dose in 24 hours is 6 mg.

4.3. CONTRAINDICATIONS

Prostin E2® should not be used in patients with a hypersensitivity to Prostin E2® or any other component of the product.

Prostin E2® should not be used in patients in whom oxytocic drugs are generally contraindicated such as:

- multiple gestation
- grand multiparity (6 or more previous term pregnancies)
- engagement of the head has not taken place
- previous uterine surgery (e.g., cesarean section, hysterotomy)
- cephalopelvic disproportion
- fetal heart rate pattern suggests incipient fetal compromise
- obstetric conditions where either maternal or fetal benefit/risk ratio favors surgical intervention

- unexplained vaginal discharge and/or abnormal uterine bleeding during current pregnancy
- nonvertex presentation

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prostin E2® products should be used with caution in patients with impaired cardiovascular, hepatic or renal function, asthma, glaucoma or raised intraocular pressure, or ruptured chorioamniotic membranes.

Continuous electronic monitoring of uterine activity and fetal heart rate should be conducted during use of Prostin E2®. Patients who develop uterine hypertonus or hypercontractility, or in whom unusual fetal heart rate patterns develop, should be managed in a manner that addresses the welfare of the fetus and mother.

As with any oxytocic agent, the risk of uterine rupture should be considered.

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 labor induction (see section **4.8. Undesirable Effects**). Therefore, in these women, use of Prostin E2® should be undertaken 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 Prostin E2® gel may result in inadvertent 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. The sequential use of oxytocin following administration of Prostin E2® cervical gel, intravaginal gel, or vaginal tablets is recommended, with a dosing interval of at least 6 hours.

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Prostin E2® is for use in pregnant women at or near term.

Prostaglandin E_2 produced an increase in skeletal anomalies in rats and rabbits. Prostin E2® has been shown to be embryotoxic in rats and rabbits, and any dose that produces sustained increased uterine tone could put the embryo or fetus at risk (see section **4.4. Special Warnings and Special Precautions for Use**).

Lactation

Prostaglandins are excreted in breast milk at very low concentrations. No measurable differences were observed in the milk of mothers delivering prematurely and at term.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable

4.8. UNDESIRABLE EFFECTS

Topical Use

Maternal Adverse Events. The following maternal adverse events have been reported with use of the cervical gel, intravaginal gel, and vaginal tablets:

Immune system disorders: Hypersensitivity reactions (e.g., Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction)

Gastrointestinal disorders: Diarrhea, nausea, vomiting

Musculoskeletal and connective tissue disorders: Back pain

Pregnancy, puerperium and perinatal conditions: Uterine contractile abnormalities (increase frequency, tone, or duration), uterine rupture

Reproductive system and breast disorders: Warm feeling in vagina

General disorders and administration site conditions: Fever

The following maternal adverse events have been reported only with use of the vaginal tablets:

Vascular disorders: Hypertension

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Pregnancy, puerperium and perinatal conditions: Abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation

Fetal Adverse Events. The following fetal adverse events have been reported with use of the cervical gel, intravaginal gel, and vaginal tablets.

Pregnancy, puerperium and perinatal conditions: Still births

Investigations: Fetal distress/altered fetal heart rate (FHR)

The following fetal adverse event has only been reported with vaginal tablets.

Pregnancy, puerperium and perinatal conditions: Neonatal death

Systemic Use

Maternal Adverse Events. The following maternal adverse events have been reported with use of the oral tablets and the sterile solution (1 mg/mL)

Immune system disorders: Hypersensitivity reactions (e.g., Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction)

Nervous system disorders: Transient vasovagal symptoms (flushing, shivering, headache, dizziness)

Cardiac disorders: Cardiac arrest

Vascular disorders: Hypertension

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Gastrointestinal disorders: Diarrhea, nausea, vomiting

Skin and subcutaneous tissue disorders: Rash

Musculoskeletal and connective tissue disorders: Back pain

Pregnancy, puerperium and perinatal conditions: Uterine contractile abnormalities (increase frequency, tone, or duration), abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation, uterine rupture

General disorders and administration site conditions: Fever

The following maternal adverse events have been reported only with use of the sterile solution (1 mg/mL):

General disorders and administration site conditions: Local tissue irritation / erythema (injection site)

Investigations: Elevated White Blood Cells (WBCs)

Fetal Adverse Events. The following fetal adverse events have been reported with use of the oral tablets and the sterile solution:

Pregnancy, puerperium and perinatal conditions: Neonatal death, still birth

Investigations: Fetal distress/altered FHR, neonatal distress/low Apgar score

Post-marketing surveillance:

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labor was induced by pharmacological means, either with Prostin E2® or oxytocin (see section **Special Warnings and**

Special Precautions for Use). The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labors).

4.9. OVERDOSE

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. Because of the transient nature of PGE_2-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. B-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PGE_2 for cervical ripening.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of Action/Effect

For uterine stimulation

Prostin E2® stimulates the myometrium of the gravid uterus to contract in a manner that is similar to the contractions seen in the term uterus during labor. Whether or not this action results from a direct effect of Prostin E2® on the myometrium has not been determined. Nonetheless, the myometrial contractions induced by the vaginal administration of Prostin E2® are sufficient to produce evacuation of the products of conception from the uterus in the majority of cases.

For cervical ripening

Prostin E2® has a local cervical effect in initiating softening, effacement, and dilation. These changes, referred to as cervical ripening, occur spontaneously as the normal pregnancy progresses toward term and allow evacuation of uterine contents by decreasing cervical resistance at the same time that myometrial activity increases.

Other actions

Prostin E2® is also capable of stimulating smooth muscle of the gastrointestinal tract in humans. This activity may be responsible for the vomiting and/or diarrhea that is occasionally seen when Prostin E2® is used for preinduction cervical ripening.

In laboratory animals, and also in humans, large doses of Prostin E2® can lower blood pressure, probably as a result of its effect on smooth muscle of the vascular system. Prostin E2® can also elevate body temperature; however, with the dose of Prostin E2® used for cervical ripening, these effects have not been seen.

5.2. PHARMACOKINETIC PROPERTIES

General characteristics of active substance

Absorption

When administered vaginally, Prostin E2® is rapidly absorbed. Peak plasma concentrations of the cervical gel formulation are achieved in 30-45 minutes. Prostin E2® is 73% bound to human plasma albumin.

The increase in prostaglandin metabolites in plasma was significantly greater with the vaginal gel than with the vaginal tablet suggesting that the gel may have greater bioavailability.

Following insertion of the vaginal tablet, PGE_2 absorption (as measured by the presence of PGE_2 metabolites) increases to reach a peak at about 40 minutes.

Following ingestion of the oral tablet, PGE_2 absorption (as measured by the presence of PGE_2 metabolites) was detectable at 15 minutes, with a peak level occurring at about 45 minutes after the first oral dose. There was little evidence of accumulative effects when a second dose was administered after one hour.

Distribution and Metabolism

Prostin E2® is widely distributed in the mother.

Intravenous administration results in very rapid distribution and metabolism, with only 3% of unchanged drug remaining in the blood after 15 minutes. At least nine prostaglandin E_2 metabolites have been identified in human blood and urine.

PGE_2 is rapidly metabolized to 13, 14-dihydro-15-keto PGE_2, which is converted to 13, 14-dihydro, 15-keto PGA_2. Prostin E2® is completely metabolized in humans. It is extensively metabolized in the lungs, and the resulting metabolites are further metabolized in the liver and kidney.

Elimination

The drug and its metabolites are excreted primarily by the kidneys, with a small amount excreted in the feces.

5.3. PRECLINICAL SAFETY DATA

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenic bioassay studies have not been conducted in animals with Prostin E2® due to the limited indications for use and short duration of administration. No evidence of mutagenicity was observed in the Micronucleus Test or Ames Assay.

6. PHARMACEUTICAL PARTICULAR

6.1. LIST OF EXCIPIENTS

Product contains Lactose
Gluten free

6.2. INCOMPATIBILITIES

Not known

6.3. SHELF LIFE

Please see pack for expiry of product.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (4°C).
Avoid exposure to heat, sunlight and moisture.

6.5. NATURE AND CONTENT OF CONTAINER

PROSTIN E2® containing 3mg Dinoprostone ; is available in the pack of 1 tablet

Prostin-E2/LPD/PK01.1
According to CDS dated: December 08, 2011; Supersedes CDS dated: March 10, 2008