PROSTIN™ E2

1. NAME(S) OF THE MEDICINAL PRODUCT

PROSTIN E2

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: dinoprostone as the naturally occurring prostaglandin E_2 (PGE_2)

Vaginal tablets containing 3 mg dinoprostone

3. PHARMACEUTICAL FORM

Vaginal Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Induction of labor in term or near-term pregnant women who have favorable induction features, and who have a singleton pregnancy with a vertex presentation.

4.2 Posology and Method of Administration

The initial dose is 1 tablet (3 mg) of dinoprostone 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.

Usage is restricted to qualified health care professionals and to hospitals and clinics with specialized 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 hemorrhage, fetal and neonatal death.

4.3 Contraindications

Dinoprostone should not be used in patients with a hypersensitivity to dinoprostone or any of the other components of the product.

Dinoprostone 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

Dinoprostone 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.

Concomitant medication, maternal and fetal status should be taken into consideration in order to minimize the risk of uterine hyperstimulation, uterine rupture, uterine hemorrhage, fetal and neonatal death.

Continuous electronic monitoring of uterine activity and fetal heart rate should be conducted during use of dinoprostone. 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 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. The sequential use of oxytocin following administration of dinoprostone vaginal tablets is recommended, with a dosing interval of at least 6 hours.

4.6 Pregnancy and Lactation

Pregnancy

Dinoprostone is for use in pregnant women at or near term.

Prostaglandin E_2 produced an increase in skeletal anomalies in rats and rabbits. Dinoprostone 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 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

Maternal Adverse Events. The following maternal adverse events have been reported with use of the 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, abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation

Reproductive system and breast disorders: Warm feeling in vagina

General disorders and administration site conditions: Fever

Vascular disorders: Hypertension

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Fetal Adverse Events. The following fetal adverse events have been reported with use of the vaginal tablets:

Pregnancy, puerperium and perinatal conditions: Fetal death, stillbirth, neonatal death

Fetal 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 Posology and Method of Administration** and **4.4 Special Warnings and Precautions for Use**).

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

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 dinoprostone or oxytocin (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 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
Dinoprostone 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 dinoprostone on the myometrium has not been determined. Nonetheless, the myometrial contractions induced by the vaginal administration of dinoprostone are sufficient to produce evacuation of the products of conception from the uterus in the majority of cases.

For cervical ripening
Dinoprostone 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
Dinoprostone 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 dinoprostone is used for preinduction cervical ripening.

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

5.2 Pharmacokinetic Properties

General characteristics of active substance

Absorption
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.

Distribution and Metabolism
Dinoprostone is widely distributed in the mother.

PGE_2 is rapidly metabolized to 13, 14-dihydro-15-keto PGE_2, which is converted to 13, 14-dihydro, 15-keto PGA_2. Dinoprostone 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 dinoprostone 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 PARTICULARS

6.1 List of Excipients

Starch, Colloidal Silicon Dioxide, Lactose, Microcrystalline Cellulose, Magnesium Stearate

6.2 Incompatibilities

No incompatibilities have been reported.

6.3 Shelf-life

Refer to outer carton for shelf-life

6.4 Special Precautions for Storage

Store in a refrigerator at 2-8°C. The tablets should be used within a month of opening.

6.5 Nature and Contents of Container

PROSTIN E2 vaginal tablets are available in packs of 4 tablets.

6.6 Instructions for Use/Handling

None

7. PRODUCT OWNER

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