Pfizer
Prostin E2®
Dinoprostone
CDS
Ethiopia, Kenya, Nigeria and Tanzania

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prostin E2 0,5 mg tablets
Prostin E2 3 mg vaginal tablets
(dinoprostone)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: dinoprostone as the naturally occurring prostaglandin E2 (PGE2)
Oral tablets containing 0.5 mg dinoprostone
Vaginal tablets containing 3 mg dinoprostone

3. PHARMACEUTICAL FORM

Vaginal Tablets
Oral Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROSTIN E2 tablets are indicated for the induction of labour at or near term in pregnant women.

4.2 Posology and method of administration

Vaginal Tablets
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.

Oral Tablets
The initial dose is 1 tablet (0.5 mg) of dinoprostone, administered with water. Subsequent doses of 1 tablet may be administered on an hourly basis. The typical single dose is 0.5 mg; however, if uterine activity is inadequate, dosage may be increased to 2 tablets (1 mg) per hour until adequate activity is established. Thereafter, a reduction to 1 tablet per hour should be considered. The maximum single dose should not exceed 3 tablets (1.5 mg).

4.3 Contraindications

Dinoprostone should not be used in patients with a hypersensitivity to dinoprostone or any other component 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.

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. The Clinician should be alert that the intracervical placement of dinoprostone 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 dinoprostone cervical gel, intravaginal gel, or 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 E2 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 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 effect

Topical Use
Maternal Adverse Events. The following maternal adverse events have been reported with use of 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 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:

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 fetal adverse events have been reported with use of the oral tablets:

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 dinoprostone or oxytocin (see section **4.4 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 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 [31]. B-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PGE2 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

When administered vaginally, dinoprostone is rapidly absorbed. Peak plasma concentrations of the cervical gel formulation are achieved in 30-45 minutes. Dinoprostone 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, PGE2 absorption (as measured by the presence of PGE2 metabolites) increases to reach a peak at about 40 minutes.

Following ingestion of the oral tablet, PGE2 absorption (as measured by the presence of PGE2 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

Dinoprostone 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 E2 metabolites have been identified in human blood and urine.

PGE2 is rapidly metabolized to 13, 14-dihydro-15-keto PGE2, which is converted to 13, 14-dihydro, 15-keto PGA2. 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

Lactose, Microcrystalline Cellulose, Colloid Silicon, Dioxide, Maize Starch, Magnesium Stearate

6.2 Incompatibilities

Not Known.

6.3 Shelf life

The vaginal tablets should be used within 1 month of opening the bottle.
Keep out of the sight and reach of children.
Do not use Prostin E2 after the expiry date which is stated on the carton/foil after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Store in refrigerator (2° - 8°C) Do not freeze.

6.5 Nature and contents of container

Aluminium foil strip of 4 tablets, each box containing 4 tablets.

6.6 Special precautions for disposal and other handling

Wash hands thoroughly with soap and water after administration.

7. FURTHER INFORMATION

MANUFACTURED BY

Sanico NV, Veedijk 59, Industriezone 4,
2300 Turnhout, Belgium.

8. PRESCRIPTION STATUS

On medical prescription only.

9. DATE OF REVISION OF THE TEXT

July 2017