Prostin E2®

Dinoprostone

Oral Tablets/ Vaginal Tablets

Reference Market: Belgium

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PROSTIN E2 0.5 mg tablets
PROSTIN E2 3 mg vaginal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROSTIN E2 0.5 mg tablets contains 0.5 mg dinoprostone in one tablet.
PROSTIN E2 3 mg vaginal tablets contains 3 mg dinoprostone in one tablet.

PROSTIN E2 0.5 mg tablets contains 185.5 mg lactose per tablet.
PROSTIN E2 3 mg vaginal tablets contains 742 mg lactose per vaginal tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PROSTIN E2 0.5 mg tablets for oral use.
PROSTIN E2 3 mg vaginal tablets for vaginal use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROSTIN E2 tablets are indicated for the induction of labour at and near the end of pregnancy in women with a mature uterine cervix and with a single pregnancy in vertex presentation. The vaginal tablets are used as an alternative to oral or parenteral administration of dinoprostone.

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.

ORAL ADMINISTRATION
PROSTIN E2 0.5 mg tablets are swallowed with some water. The dose of PROSTIN E2 should be adjusted to the individual patient's reaction. The lowest dose of PROSTIN E2 that induces adequate uterine contractions and/or a normally progressing cervical opening should always be attempted. The initial dose is 0.5 mg (1 tablet) PROSTIN E2. Subsequently the drug is administered every hour, the usual dose being 0.5 mg (1 tablet). If the induced uterine activity is not sufficient, a dose of 1 mg (2 tablets) can be administered every hour until uterine contractions have become efficient. However, it is recommended not to exceed a dose of 1.5 mg (3 tablets) per administration. Once the dilatation is well under way, it is usually possible to reduce the dose again to 0.5 mg (1 tablet) every hour.
Continuous administration of the drug for more than 2 days is not recommended.

VAGINAL ADMINISTRATION
The dose of PROSTIN E2 3 mg vaginal tablets should be adjusted to the individual patient's response. In normal circumstances one vaginal tablet should be introduced high in the posterior vaginal fornix.
If labour has not started after 6 to 8 hours, a second tablet may be introduced. The maximum daily dose of 6 mg of dinoprostone (2 vaginal tablets) should not be exceeded. The treatment can be repeated the following day. If labour has not started after 48 hours, another treatment should be considered.

Paediatric population

The safety and efficacy of PROSTIN E2 in paediatric patients has not been established. There is no relevant use of PROSTIN E2 in paediatric patients other than adolescents.

4.3 Contraindications

Administration of PROSTIN E2 is contraindicated:

1. in patients with a hypersensitivity to dinoprostone or to any of the excipients listed in section 6.1;
2. in patients in whom oxytocic drugs are generally contraindicated, in cases of:
   - multiparity (six or more previous term pregnancies)
   - engagement of the head has not taken place
   - previous uterine surgery (after caesarean section, hysterotomy etc.)
   - cephalopelvic disproportion
   - fetal heart rate pattern suggests incipient fetal compromise
   - obstetric conditions where either maternal or fetal risk/benefit ratio favours surgical intervention
   - unexplained vaginal discharge and/or abnormal uterine bleeding during current pregnancy
   - nonvertex presentation
   - antecedents of difficult and/or traumatic delivery

4.4 Special warnings and precautions for use

- This product is destined for use in hospital only and administered under medical surveillance.
- A vaginal examination should be carried out prior to administering PROSTIN E2.
- 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 abnormal foetal heart rate patterns develop, should be managed in a manner that addresses the welfare of the foetus and mother.
- Dinoprostone should be used with caution in patients with impaired cardiovascular, hepatic or renal function, asthma, glaucoma or raised intraocular pressure, or ruptured chorioamniotic membranes. Dinoprostone should be used with caution in patients with multiple pregnancy.
- 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.
- PROSTIN E2 should only be administered by physicians having an adequate obstetric infrastructure available (including equipment to control the haemodynamic functions) as well as the possibility to rapidly intervene surgically in the event of possible danger for the mother or the child.
- If the effect of PROSTIN E2 appears to be excessive (e.g., hypertonicity of the uterus with or without foetal bradycardia), tocolytics (e.g., fenoterol) may be useful.
- Until adequate data are available, the use of PROSTIN E2 in pathological pregnancies, i.e., with a statistically increased foetal risk (e.g., hypertension, diabetes, toxicosis, postdate pregnancy, etc.) should be avoided as a precautionary measure.
- Animal studies with the administration of high doses for several weeks, have demonstrated that prostaglandins of the E and F series can cause proliferation of the bone. A similar effect is seen in newly born babies treated with prostaglandin E_1 for prolonged periods of time. These effects on the bone have not been demonstrated following administration of PROSTIN E2 for short periods of time.
- The induction of labour in general is associated with the risk of amniotic fluid embolism (AFE) (also called Anaphylactoid syndrome of pregnancy). Cases of AFE have been reported after the use of different formulations of dinoprostone for cervical maturation (see section 4.8). The onset is often abrupt during labour and delivery/caesarean section or up till 48 hours post-partum.
- The clinician should be alert that the intracervical placement of dinoprostone 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).

- Severe cardiovascular accidents, potentially fatal (myocardial infarction and/or ventricular fibrillation) have been reported with prostaglandins and prostaglandin analogues for injection. The risk of such accidents increases with age, chronic smoking and recent smoking. As a precautionary measure, female patients should be asked not to smoke during the days prior to dinoprostone administration.

Lactose
PROSTIN E2 tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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. Since oxytocin and dinoprostone act on different receptors of the uterine smooth muscle cells, concomitant administration of both drugs can lead to increased contractility of the myometrium. It is recommended to carefully monitor the patient if these drugs are used in sequence.

4.6 Fertility, pregnancy and lactation

Fertility
There are no clinical data on the effects of dinoprostone on fertility.

Pregnancy
PROSTIN E2 is indicated for treatment of pregnant women for use before term or during delivery.
Any dose that produces sustained increased uterine tone could put the embryo or fetus at risk (see sections 4.4 and 4.8).

Animal studies have shown reproductive toxicity (see section 5.3).

Breastfeeding
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 relevant.

4.8 Undesirable effects

ORAL ADMINISTRATION

Safety profile

The most commonly reported adverse drug reactions in clinical trials for oral formulation of dinoprostone (occurring in >10% of patients) are diarrhoea, nausea, vomiting in the mother, abnormal uterine contractions, low APGAR score and abnormal foetal heart rate in the infant.
Other adverse events reported in up to 10% of patients are vasovagal symptom (flushing, shivering, headache, dizziness), hypertension and foetal distress syndrome.

Tabulated list of adverse reactions

The table below lists the adverse effects by System Organ Class (SOC) and frequency. Within each frequency grouping, adverse events are presented in order of decreasing seriousness. Frequencies are defined as: 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), or not known (cannot be estimated from the available data).

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				Disseminated intravascular coagulation		
Immune system disorders						Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction (including anaphylactoid syndrome of pregnancy), Hypersensitivity
Nervous system disorder		Vasovagal symptom (flushing, shivering, headache, dizziness)				
Cardiac disorders						Cardiac arrest
Vascular disorders		Hypertension	Hypotension			
Respiratory, thoracic and mediastinal disorders			Bronchospasm			Asthma, Pulmonary oedema, Dyspnoea, Apnoea
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting					
Skin and subcutaneous tissue disorders			Rash			
Musculoskeletal, and connective tissue disorders						Back pain
Pregnancy, puerperium and perinatal conditions	Uterine contractions abnormal	Foetal distress syndrome	Abruptio placentae			Rapid cervical dilatation, Amniotic fluid embolism, Uterine rupture, Foetal death[§], Stillbirth[§], Neonatal death[§], Neonatal distress
General disorders and administration site conditions			Pyrexia			

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Investigations	APGAR score low, Foetal heart rate abnormal					

§ 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).

VAGINAL ADMINISTRATION

Safety profile

The most commonly reported adverse drug reactions in clinical trials for topical formulations of dinoprostone (occurring in >10% of patients) are vomiting in the mother and abnormal foetal heart rate in the infant.
Other adverse events reported in up to 10% of patients are nausea, back pain, abnormal uterine contractions, vulvovaginal burning sensation, pyrexia and foetal distress syndrome.

Tabulated list of adverse reactions

The table below lists the adverse effects by System Organ Class (SOC) and frequency. Within each frequency grouping, adverse events are presented in order of decreasing seriousness. Frequencies are defined as: 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), or not known (cannot be estimated from the available data).

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				Disseminated intravascular coagulation		
Immune system disorders						Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction (including anaphylactoid syndrome of pregnancy), Hypersensitivity
Cardiac disorders						Cardiac arrest
Vascular disorders						Hypotension, Hypertension
Respiratory, thoracic and mediastinal disorders						Asthma, Bronchospasm, Pulmonary embolism, Pulmonary oedema, Dyspnoea, Apnoea
Gastrointestinal disorders	Vomiting	Nausea				Diarrhoea

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Musculoskeletal, and connective tissue disorders		Back pain				
Pregnancy, puerperium and perinatal conditions		Uterine contractions abnormal				Abruptio placentae, Amniotic fluid embolism, Rapid cervical dilatation, Uterine rupture, Foetal death[§], Stillbirth[§], Neonatal death[§]
Reproductive system and breast disorders		Vulvovaginal burning sensation				Vaginal irritation
General disorders and administration site conditions		Pyrexia				Headache
Investigations	Foetal heart rate abnormal	Foetal distress syndrome				

[§] 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).

Post-marketing surveillance

Blood and lymphatic system disorders: 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).

Pregnancy, puerperium and perinatal conditions: Labour induction has been associated with the risk of anaphylactoid syndrome of pregnancy (amniotic fluid embolism (AFE)) (see section 4.4). The precise physiopathology of AFE remains unexplained but the crossing of amniotic liquid components into the maternal circulation has been incriminated in the occurrence of an anaphylactoid reaction and mechanical obstruction of the pulmonary capillaries leading to major hemodynamic, haemorrhagic and neurological problems. The most frequently reported clinical signs are acute hypotension, cardiac arrest, cardiac arrhythmias, agitation-type prodromes and sensation of malaise, convulsions, cyanosis, dyspnoea or acute respiratory distress, foetal distress, maternal haemorrhage associated in the majority of the cases to a disseminated intravascular coagulation. These clinical signs can appear separately or in combination.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing 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 according to their local country requirements.

4.9 Overdose

The main signs of an excessive reaction to PROSTIN E2 tablets are hypercontractility or hypertonicity of the myometrium, possibly leading to foetal distress. The treatment of an excessive reaction of the myometrium consists of removing the drug from the vagina, putting the patient in a lateral semi-supine position and the administration of oxygen.
Since clinical studies with prostaglandin antagonists are not sufficiently advanced to allow for recommendations to be made, an overdose should at present be treated symptomatically.

If uterine overstimulation (and/or foetal distress) is not resolved by discontinuation of the treatment, intravenous administration of a beta-2-mimetic can be useful. If tocolytic treatment is also unsuccessful, immediate delivery is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: oxytocic drugs
ATC code: G02AD02

Dinoprostone or prostaglandin E_2 (PGE_2) belongs to a family of natural unsaturated fatty acids.
Prostaglandins have very diverse pharmacodynamic properties, including the possibility to stimulate organs containing smooth muscle fibres and modulating the response of organs to other hormonal stimuli. It was observed that dinoprostone induces rhythmical contractions of the uterus that can expel the contents of the uterus if they are maintained for a sufficiently long period of time. Dinoprostone, contrary to oxytocin, acts on the uterus at any time during pregnancy and has no antidiuretic effect.
In the first and second trimester of pregnancy the pregnant woman is less sensitive to dinoprostone than in the last trimester.

5.2 Pharmacokinetic properties

Natural prostaglandins are rapidly produced from the corresponding free poly-unsaturated fatty acids. These substances induce significant changes, even in minimal amounts. Dinoprostone is completely metabolized. The metabolism takes place mainly in the lungs. The main route of elimination is via the kidneys.
The half-life of dinoprostone is very short (less than 1 minute following intravenous administration). The metabolites, of which 13,14-dihydro-15-keto-PGE2 is the main one, are far less active and have a half-life of some 8 minutes.

ORAL ADMINISTRATION
The resorption is complete approximately 1 hour after oral administration. Peripheral plasma levels of dinoprostone remain constant.
Peak plasma levels of 13,14-dihydro-15-keto-PGE2 are obtained 30 to 60 minutes following oral administration.

VAGINAL ADMINISTRATION
Peak plasma levels of the main metabolites are obtained 3 to 4 hours following the administration.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

There was some evidence of a low level of teratogenic activity, with skeletal abnormalities observed in the rat when dams were dosed subcutaneously at 3.3 mg/kg/day. There was also evidence of embryotoxicity, likely mediated as a result of increased uterine tone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (see section 4.4 – Lactose), microcrystalline cellulose, anhydrous colloidal silica, maize starch, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use PROSTIN E2 after the expiry date which is stated on the carton / Blister/ Bottle label after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

6.5 Nature and contents of container

PROSTIN E2 0.5 mg tablets: 10 tablets in an amber glass bottle type III.
PROSTIN E2 3 mg vaginal tablets: 4 tablets in strip.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER
Pfizer SA, Boulevard de la Plaine 17, 1050 Brussels, Belgium.

MANUFACUTRED BY
Sanico NV.Veedijk 59,2300 Turnhout, Belgium.

8. PRESCRIPTION STATUS

Medicinal product subject to medical prescription.

9. DATE OF REVISION OF THE TEXT

August 2021**....**

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach of children

Council of Arab Health Ministers
Union of Arabic Pharmacists