PROSTIN E2

0.75 mg
5 mg

Dinoprostone

Concentrate for solution for infusion

Reference Market: Belgium

AfME Markets using same as LPD:

Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PROSTIN E2 0.75 mg concentrate for solution for infusion
PROSTIN E2 5 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROSTIN E2 0.75 mg concentrate for solution for infusion contains 1 mg dinoprostone in 1 ml solution.
PROSTIN E2 5 mg concentrate for solution for infusion contains 10 mg dinoprostone in 1 ml solution.

Excipient with known effect: anhydrous ethanol
PROSTIN E2 0.75 mg contains 600 mg of alcohol (ethanol) in each 0.75 ml ampoule which is equivalent to 800 mg/ml (80% w/v).
PROSTIN E2 5 mg contains 400 mg of alcohol (ethanol) in each 0.5 ml ampoule which is equivalent to 800 mg/ml (80% w/v).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROSTIN E2 is indicated for the following indications:
A. Artificial induction of labor.
PROSTIN E2 0.75 mg concentrate for solution for infusion à 1 mg/ml:
1. Therapeutic induction of labor when there are no foetal or maternal contraindications.
2. Induction of labor in cases of fetal death in utero.

B. Management of fetus retention and hydatidiform mole.
PROSTIN E2 5 mg concentrate for solution for infusion à 10 mg/ml:
1. PROSTIN E2 can be used for evacuation of the uterine content in cases of fetus retention (spontaneous abortion).
2. PROSTIN E2 is useful as non-surgical treatment for the evacuation of hydatidiform mole.

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.

DIRECTIONS FOR THE PREPARATION OF DILUTED SOLUTIONS

A. From the 1 mg/ml concentrate for solution for infusion:
For intravenous use for the induction of labor (1.5 micrograms/ml dilute infusion).
For use by IV drip (a drip set delivering 60 drops per ml must be used) or constant rate infusion pump: withdraw 0.75 ml of the 1 mg/ml preparation using an aseptic technique, and add to 500 ml sterile normal saline or 5% sterile aqueous dextrose solution. Shake to ensure uniformity. Diluted solution must be used within 24 hours of preparation.

B. From the 10 mg/ml concentrate for solution for infusion:
For intravenous use for fetus retention and hydatidiform mole (5.0 micrograms/ml dilute infusion).
For use by IV drip (a drip set delivering 60 drops per ml must be used) or a constant rate infusion pump: withdraw 0.5 ml of the 10 mg/ml preparation using an aseptic technique, and add to 1000 ml sterile normal saline or 5% sterile aqueous dextrose solution (or 0.25 ml to 500 ml). Shake to ensure uniformity. Diluted solution must be used within 24 hours of preparation.

POSOLOGY
In all cases the dose should be adapted to the patient.

1. For induction of labor by the intravenous route (1.5 micrograms/ml diluted solution for infusion):
The initial rate of infusion should be 0.25 micrograms/min, which should be maintained for at least the first 30 minutes. If a satisfactory uterine contractility response is produced, this rate should be maintained. If not, the rate may be increased to 0.5 micrograms/min. In some circumstances, after a fair trial (one or two hours), the rate may be increased to 1.0 micrograms/min or, rarely, 2.0 micrograms/min to produce a satisfactory contractility, but increases should be made in the light of undesirable effects and uterine response. If uterine hypertonus or fetal distress occurs, the infusion should be stopped until the condition of the patient and the fetus returns to normal. The infusion may then be recommended at 50% of the last dose level and subsequently increased with caution. Cases of foetal death in utero may require higher doses than those given above. An initial rate of 0.5 micrograms/min may be used with gradual increases at intervals of not less than one hour as described above. Undesirable effects permitting, the final rate of infusion may be increased to 4.0 micrograms/min if uterine contractility response is inadequate at the lower dosage rates. Continuous administration of the drug for more than two days is not recommended.
2. For the management of fetus retention and hydatidiform mole by the intravenous route (5.0 mcg/ml diluted solution for infusion):
The initial rate of infusion will be 2.5 micrograms/min, and this rate should be maintained for at least the first 30 minutes. If satisfactory uterine contractility response is produced, this rate should be maintained; if not, the rate should be increased to 5 micrograms/min. If satisfactory uterine activity is not produced after at least 4 hours at this rate of infusion, the rate may be increased up to 10 micrograms/min, undesirable effects permitting, and maintained until evacuation of the uterine content occurs or the treatment is considered a failure. If significant undesirable effects occur, the rate of infusion should be decreased by 50% or discontinued.
Dependent on the type of infusion pump, a different concentration of solution (e.g. 15 micrograms/ml) may be required, but the infused dose rate (mcg/min) should remain as above.

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 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 case of :

– multiparity (six or more previous term pregnancies);
– engagement of the head has not taken place;
– previous uterine surgery (after cesarean section, hysterectomy, etc.);

- 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;
- non-vertex presentation
- vascular pathology (in particular coronary disease);
- heart-decompensation, severe continuous arterial hypertension;
- history of difficult and/or traumatic delivery..

4.4 Special warnings and precautions for use

This product is for use in hospitals only and administered under medical surveillance.

Patients with known pelvic infections should first of all receive adequate treatment.

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.

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.

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.
Consequently it is necessary:

- To take into account these risks in female patients over 35 years old and in women who smoke;
- To take into account other cardiovascular risk factors (hyperlipidemia, diabetes, family history);
- In the event of suspected coronary spasm (thoracic pain, rhythm disorders, significant arterial hypotension, cardiovascular collapse, fainting) an ECG must be performed immediately;
- If the ECG confirms diagnosis of coronary spasm, it is necessary to use injectable nitrate derivatives or injectable calcium antagonists as rapidly as possible since antithrombotic treatment is not appropriate for this kind of disorder.

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.

In labor induction, cephalopelvic compatibility must be carefully evaluated before use of PROSTIN E2. Labor progression (dilatation, engagement) must be closely monitored during, and certainly also after the induction.

The use of PROSTIN E2 concentrate for solution for infusion is restricted to large, well equipped obstetric clinics with competent and permanently available medical and paramedical staffs.

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.

Excipient information
PROSTIN E2 0.75 mg contains 600 mg of alcohol (ethanol) in each 0.75 ml ampoule which is equivalent to 800 mg/ml (80% w/v) (see section 2). The amount in each 0.75 ml ampoule of this medicine is equivalent to less than 15 ml beer or 6 ml wine.
PROSTIN E2 5 mg contains 400 mg of alcohol (ethanol) in each 0.5 ml ampoule which is equivalent to 800 mg/ml (80% w/v) (see section 2). The amount in each 0.5 ml ampoule of this medicine is equivalent to less than 10 ml beer or 4 ml wine.

The small amount of alcohol in this medicine will not have any noticeable effects, certainly not after dilution.

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.

Therefore, it is recommended to carefully monitor the patient if these drugs are used in sequence. Because prostaglandins have multiple pharmacological effects, simultaneous administration of NSAIDs or other substances altercating on prostaglandins metabolism requires special caution.

4.6 Fertility, pregnancy and lactation

Fertility
There are no clinical data available 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 foetus at risk (see sections 4.4 and 4.8).

Animal studies have confirmed reproductive toxicity (see section 5.3)

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 relevant.

4.8 Undesirable effects

Safety profile

The most commonly reported adverse drug reactions in clinical trials for intravenous formulation of dinoprostone (occurring in >10% of patients) are diarrhoea, nausea, vomiting in the mother, abnormal uterine contractions, injection site erythema, injection site irritation, 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)	Convulsion			
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			

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	Foetal distress syndrome	Abruptio placentae			Amniotic fluid embolism, Uterine rupture, Rapid cervical dilatation, Foetal death[§], Stillbirth[§], Neonatal death[§]
General disorders and administration site conditions	Injection site erythema, Injection site irritation		Pyrexia			
Investigations	APGAR score low, Foetal heart rate abnormal					White blood cell count increased

[§] 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).

- **Management of fetal retention, and hydatidiform mole (10 mg/ml).**

Clinical studies have shown that recommended dosages did not induce life threatening undesirable effects. When seen, undesirable effects have generally been dose-dependent, transient, and reversible on discontinuation of therapy.

- **In isolated cases:** in predisposed patients bronchoconstriction can occur.

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

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 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.

To Report side effects

- Saudi Arabia

National Pharmacovigilance Centre (NPC)
- Call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

Other GCC States

- *Please contact the relevant competent authority.*

4.9 Overdose

Symptoms of overdosage may be uterine hypercontractility or 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.
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: oxytocics
ATC code: G02AD02

Dinoprostone or prostaglandin E2 belongs to a family of naturally occurring unsaturated fatty acids. Prostaglandins possess a wide range of pharmacological activities, including the ability to stimulate smooth muscle containing organs and to modulate organ responses to other hormonal stimuli. Dinoprostone induces rhythmical uterine contractions which, if continued for a sufficient time, are capable of expelling the uterine content.
In contrast with oxytocin, dinoprostone is influencing the uterine activity on every given time during pregnancy and has no antidiuretic effect.
Sensitivity of the pregnant woman to dinoprostone is lower during first and second trimester of the pregnancy than during last trimester.

5.2 Pharmacokinetic properties

Natural prostaglandins are produced very quickly from corresponding free polyunsaturated fatty acids. Even in minimal amounts, these substances induce significant modifications, after which they are rapidly converted into non-active metabolites. After intravenous injection, the half-life of dinoprostone is less than one minute, whereas the half-life of all its primary metabolites is about eight minutes.

5.3 Preclinical safety data

Non-clinical data resulting from conventional safety pharmacology, repeated administration toxicology and genotoxicity studies did not show any particular risk to humans.

In rats, when the mother received subcutaneous daily doses of 3.3 mg/kg/day, some slight teratogenic effects, causing skeletal abnormalities, were observed. Also, evidence of embryotoxicity has also been observed, probably resulting from the increased uterine tone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous ethanol (see section 4.4 – Excipient information).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use PROSTIN E2 after the expiry date which is stated on the Ampoule 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°-8°C).
Keep out of the sight and reach of children.

6.5 Nature and contents of container

PROSTIN E2 0.75 mg concentrate for solution for infusion: 1 ampoule with 0.75 ml solution 1 mg/ml.
PROSTIN E2 5 mg concentrate for solution for infusion: 1 ampoule with 0.5 ml solution 10 mg/ml.

Not all presentations may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with current requirements.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Pfizer S.A., 17 Boulevard de la Plaine, 1050 Brussels, Belgium.

MANUFACUTRED, PACKED & RELEASED BY

Pfizer Manufacturing Belgium N.V, Rijsweg 12, Puurs, Belgium

8. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Add the date of first authorization (01-Mar-1900).

9. DATE OF REVISION OF THE TEXT

August 2021