SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prostin® E2 3 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3 mg dinoprostone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal tablet.

White tablet marked with "UPJOHN" and "715" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxytocic. Prostin E2 Vaginal Tablets are indicated for the induction of labour, especially in patients with favourable induction features, when there are no foetal or maternal contra-indications.

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.

Posology

One tablet (3 mg) to be inserted high into the posterior fornix. A second tablet may be inserted after six to eight hours if labour is not established. Maximum dose 6 mg.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
Prostin E2 Vaginal Tablets should not be used where the patient is sensitive to prostaglandins or other constituents of the tablet.

Prostin E2 Vaginal Tablets are not recommended in the following circumstances:

- For patients in whom oxytocic drugs are generally contra-indicated or where prolonged contractions of the uterus are considered inappropriate such as:
- Cases with a history of Caesarean section or major uterine surgery.
- Cases where there is cephalopelvic disproportion.

- Cases in which foetal malpresentation is present.
- Cases where there is clinical suspicion or definite evidence of pre-existing foetal distress.
- Cases in which there is a history of difficult labour and/or traumatic delivery.
- In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been instituted.
- In patients where there is clinical suspicion or definite evidence of placenta praevia or unexplained vaginal bleeding during this pregnancy.
- Patients with active cardiac, pulmonary, renal or hepatic disease.

4.4 Special warnings and precautions for use

This product is only available to hospitals and clinics with specialised obstetric units and should only be used where 24-hour resident medical cover is provided.

Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

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. Careful and regular 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.

Caution should be exercised in the administration of Prostin E2 Vaginal Tablets for the induction of labour in patients with:

- asthma or a history of asthma
- epilepsy or a history of epilepsy
- glaucoma or raised intra-ocular pressure
- compromised cardiovascular, hepatic, or renal function
- hypertension.
- ruptured chorioamniotic membranes.

Dinoprostone should be used with caution in patients with multiple pregnancy.

In labour induction, cephalopelvic relationships should be carefully evaluated before use of Prostin E2 Vaginal Tablets. During use, uterine activity, foetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus, sustained uterine contractions, or foetal distress.

In cases where there is a known history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the foetus (where applicable) should be continuously monitored throughout labour. The possibility of uterine rupture should be borne in mind where high-tone uterine contractions are sustained.

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.

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. If used in sequence, the patient's uterine activity should be carefully monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Prostin E2 Vaginal Tablets are only used during pregnancy, to induce labour.

Breast-feeding

Prostaglandins are excreted in breast milk. This is not expected to be a hazard given the circumstances in which the product is used.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: 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); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Adverse Reactions

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1 000 to <1/100	Rare ≥1/10 000 to <1/1000	Very Rare <1/10 000	Frequency Not Known (Cannot Be Estimated From Available Data)
Blood and lymphatic system disorders				Disseminated intravascular coagulation*		
Immune system disorders						Hypersensitivity, Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction
Cardiac disorders						Cardiac arrest
Vascular disorders						Hypertension**
Respiratory, thoracic and mediastinal disorders						Asthma**, Bronchospasm**
Gastrointestinal disorders	Vomiting	Nausea				Diarrhoea
Skin and subcutaneous tissue disorders						Rash
Musculoskeletal and connective tissue disorders		Back pain				

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1 000 to <1/100	Rare ≥1/10 000 to <1/1000	Very Rare <1/10 000	Frequency Not Known (Cannot Be Estimated From Available Data)
Pregnancy, Puerperium and Perinatal conditions		Uterine hypertonus, Foetal distress syndrome, Uterine contractions abnormal				Uterine rupture, Premature separation of placenta, Anaphylactoid syndrome of pregnancy**, Rapid cervical dilatation, Neonatal distress, Death neonatal††, Stillbirth†, Foetal death
Reproductive system and breast disorders		Vulvovaginal burning sensation				Irritation, Pain
General disorders and administration site conditions		Pyrexia				
Investigations	Foetal heart rate abnormal†					Apgar score low

* Reported during post marketing surveillance
** Maternal adverse events that have been reported only with use of the vaginal tablets.
† Foetal adverse events that have been reported with use of the cervical gel, intravaginal gel and vaginal tablets.
†† Foetal adverse event has only been reported with vaginal tablets.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. During use, uterine activity, foetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus, sustained uterine contractions, or foetal distress. Because of the transient nature of prostaglandin E_2 (PGE_2)-induced myometrial hyperstimulation, non-specific, conservative management was found to be effective in the vast majority of cases: i.e. maternal position change and administration of oxygen to the mother. If conservative management is not effective, ß-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PGE_2 for cervical ripening, in appropriate patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prostaglandins, ATC-code: G02AD02

Dinoprostone is a prostaglandin of the E series with actions on smooth muscle; the endogenous substance is termed prostaglandin E_2. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act predominantly as a vasodilator on blood vessels and as a bronchodilator on bronchial muscle. It is postulated that vaginal absorption of PGE_2 stimulates endogenous PGE_2 and $PGF_{2\alpha}$ production, similar to that which is seen in spontaneous labour.

5.2 Pharmacokinetic properties

Following insertion of the tablet, PGE_2 absorption (as measured by the presence of PGE_2 metabolites) increases to reach a peak at about 40 minutes. PGE_2 is rapidly metabolised to 13, 14-dihydro, 15-keto PGE_2 which is converted to 13, 14-dihydro, 15-keto PGA_2 which binds covalently to albumen.

There has been found to be inter-patient variability regarding systemic absorption of PGE_2. This can be attributed to different conditions of the vaginal mucosa between patients.

5.3 Preclinical safety data

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce proliferation of bone. Such effects have also been noted in newborn infants who received prostaglandin E_1 during prolonged treatment. There is no evidence that short-term administration of prostaglandin E_2 can cause similar bone effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Microcrystalline Cellulose
Maize Starch
Magnesium Stearate
Colloidal Anhydrous Silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator at 2-8°C.

6.5 Nature and contents of container

Aluminium foil strip containing 4 tablets.

6.6 Special precautions for disposal and other handling

Wash hands thoroughly with soap and water after administration.

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

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach

8. MARKETING AUTHORISATION NUMBER

047-33-23230

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