1. NAME OF THE MEDICINAL PRODUCT

PROPESS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal delivery system consists of a non-biodegradable polymeric drug delivery device containing 10 mg dinoprostone (Prostaglandin E_2) dispersed throughout its matrix and releases approximately 0.3mg/hour dinoprostone over 24-hour period.
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Vaginal delivery system
PROPESS is presented as a 0.8 mm thin, flat semi-transparent polymeric vaginal delivery system which is rectangular in shape (29mm by 9.5mm) with rounded corners contained within a knitted polyester retrieval system.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Initiation and / or continuation of cervical ripening in patients, at term (from 37 completed weeks of gestation) with bishop score of 6 or less.

4.2 Posology and method of administration

PROPESS should only be administered by qualified healthcare personnel in hospitals and clinics with specialised obstetric units with facilities for continuous fetal and uterine monitoring.
After insertion, uterine activity and fetal condition must be carefully and regularly monitored.

Posology

One vaginal delivery system is administered high into the posterior vaginal fornix.
The vaginal delivery system should be removed after 24 hours irrespective of whether cervical ripening has been achieved.
A dosing interval of at least 30 minutes is recommended for the sequential use of oxytocin following the removal of the vaginal delivery system. Only one application of PROPESS is recommended.

Paediatric population

The safety and efficacy of PROPESS in pregnant woman aged less than 18 years has not been established. No data are available.

Method of administration

Administration

PROPESS should be removed from the freezer just prior to the insertion.
No thawing is required prior to use.
There is a “tear mark” on side of the foil sachet. Open the package along the tear mark across the top of the sachet. Do not use scissors or other sharp objects which may cut the retrieval system.
The vaginal delivery system should be inserted high into the posterior vaginal fornix using only small amounts of water soluble lubricants to aid insertion. After the vaginal delivery system has been inserted, the withdrawal tape may be cut with scissors always ensuring there is sufficient tape outside the vagina to allow removal. No attempt should be made to tuck the end of the tape into the vagina as this may make retrieval more difficult.
The patient should be recumbent for 20 minutes to 30 minutes after insertion. As dinoprostone will be released continuously over a period of 24 hours, it is important to monitor uterine contractions and fetal condition at frequent regular intervals.

Removal

The vaginal delivery system can be removed quickly and easily by gentle traction on the retrieval tape. It is necessary to remove the vaginal delivery system to terminate drug administration when cervical ripening is judged to be complete or for any of the reasons listed below.

1. Onset of labour. For the purposes of induction of labour with PROPESS, the onset of labour is defined as the presence of regular painful uterine contractions occurring every 3 minutes irrespective of any cervical change.

There are two important points to note:

(i) Once regular, painful contractions have been established with PROPESS they will not reduce in frequency or intensity as long as PROPESS remains in situ because dinoprostone is still being administered.
(ii) Patients, particularly multigravida, may develop regular painful contractions without any apparent cervical change. Effacement and dilatation of the cervix may not occur until uterine activity is established. Because of this, once regular painful uterine activity is established with PROPESS in-situ, the vaginal delivery system should be removed irrespective of cervical state to avoid the risk of uterine hyperstimulation.

2. Spontaneous rupture of the membranes or amniotomy.
3. Any suggestion of uterine hyperstimulation or hypertonic uterine contractions.
4. Evidence of fetal distress.
5. Evidence of maternal systemic adverse dinoprostone effects such as nausea, vomiting, hypotension or tachycardia.
6. At least 30 minutes prior to starting an intravenous infusion of oxytocin, as there is a much greater risk of hyperstimulation if the dinoprostone source is not removed before administration of oxytocin.

The opening on one side of the retrieval device is present only to allow the manufacturer to enclose the vaginal delivery system into the retrieval device during manufacture. The vaginal delivery system should NEVER be removed from the retrieval device.
Upon removal of the product from the vagina, the vaginal delivery system will have swollen to 2-3 times its original size and be pliable.

4.3 Contraindications

PROPESS should not be used or left in place:

1. When labour has started.
2. When oxytocic drugs and/or other labour induction agents are being given.
3. When strong prolonged uterine contractions would be inappropriate such as in patients:

a. who have had previous major uterine surgery, e.g. caesarean section, myomectomy etc (see sections 4.4 and 4.8)
b. who have had previous major uterine cervix surgery (e.g. other than biopsies and cervical abrasion) or rupture of the uterine cervix
c. with cephalopelvic disproportion
d. with fetal malpresentation
e. with suspicion or evidence of fetal distress

4. When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted.
5. When there is hypersensitivity to dinoprostone or to any of the excipients listed in section 6.1.
6. When there is placenta previa or unexplained vaginal bleeding during the current pregnancy.

4.4 Special warnings and special precautions for use

The condition of the cervix should be assessed carefully before PROPESS is used. After insertion, uterine activity and fetal condition must be monitored carefully and regularly by qualified healthcare personnel. PROPESS must only be used in hospitals and clinics with specialised obstetric units with facilities for continuous fetal and uterine monitoring. If there is any suggestion of maternal or fetal complications or if adverse effects occur, the vaginal delivery system should be removed from the vagina.
Uterine rupture has been reported in association with the use of PROPESS, mainly in patients with contraindicated conditions (see section 4.3). Therefore, PROPESS should not be administered to patients with a history of previous caesarean section or uterine surgery given the potential risk for uterine rupture and associated obstetrical complications.
If uterine contractions are prolonged or excessive, there is possibility of uterine hypertonus or rupture and the vaginal delivery system should be removed immediately.
A second dose of PROPESS is not recommended, as the effects of a second dose have not been studied.
PROPESS should be used with caution in patients with a previous history of uterine hypertonus, glaucoma or asthma.
The experience of PROPESS in patients with ruptured membranes is limited. Therefore, PROPESS should be used with caution in those patients. Since the release of dinoprostone from the insert can be

affected in the presence of amniotic fluid, special attention should be given to uterine activity and fetal condition.
Women aged 35 and over, women with complications during pregnancy, such as gestational diabetes, arterial hypertension and hypothyroidism, and women at gestational age above 40 weeks have a higher post-partum risk for developing disseminated intravascular coagulation (DIC). These factors may additionally enhance the risk of disseminated intravascular coagulation in women with pharmacologically induced labour (see section 4.8). Therefore, uterotonic drugs, such as dinoprostone should be used with caution in these women. In the immediate post-partum phase the physician should look out carefully for early signs of a developing DIC (e.g fibrinolysis).
The Clinician should be alert that, as with other labour induction methods, use of dinoprostone may result in inadvertent abruption of placenta and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).
PROPESS should be used with caution when there is a multiple pregnancy. No studies in multiple pregnancy have been performed.
PROPESS should be used with caution when the woman has had more than three full term deliveries. No studies in woman with more than three full term deliveries have been performed.
Medication with non-steroidal anti-inflammatory drugs, including acetylsalicylic acid, should be stopped before administration of dinoprostone.
The use of the product in patients with diseases which could affect the metabolism or excretion of dinoprostone, e.g. lung, liver or renal disease, has not been specifically studied. The use of the product in such patients is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No dedicated interaction studies have been performed with PROPESS.
Prostaglandins potentiate the uterotonic effect of oxytocic drugs. Therefore, PROPESS should not be used concurrently with the use of oxytocic drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy

PROPESS should not be used during pregnancy prior to 37 completed weeks of gestation.

Breast-feeding

No studies have been performed to investigate the amount of dinoprostone in colostrum or breast milk following the use of PROPESS.
Dinoprostone may be excreted in colostrum and breast milk, but the level and duration is expected to be very limited and should not hinder breastfeeding. No effects on the breastfed new-borns have been observed in the clinical studies conducted with PROPESS.

Fertility

Not relevant

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of safety profile**:**
The most commonly reported adverse drug reactions in placebo-controlled and active comparator efficacy clinical trials (N=1116) were “fetal heart rate disorder” (6.9%), “uterine contractions abnormal” (6.2%) and “abnormal labour affecting foetus” (2.6 %).

The table below displays the main ADRs distributed by system organ classes (SOC) and frequency. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

Adverse reactions observed in clinical studies are presented according to their incidence, post authorisation reported adverse reactions are presented in the column frequency unknown.

System organ class	**Common (≥ 1/100 and < 1/10)**	**Uncommon (≥ 1/1000 and ≤ 1/100)**	**Not known: frequency cannot be estimated from the available data**
Blood and lymphatic system disorders			Disseminated intravascular coagulation

System organ class	Common (≥ 1/100 and < 1/10)	Uncommon (≥ 1/1000 and ≤ 1/100)	Not known: frequency cannot be estimated from the available data
Immune system disorders			Anaphylactic reaction Hypersensitivity
Nervous system disorders		Headache	
Cardiac disorders	Fetal heart rate disorder [1*]		
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Neonatal respiratory distress related conditions	
Gastrointestinal disorders			Abdominal pain, Nausea, vomiting, diarrhoea
Hepatobiliary disorders		Neonatal hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Pruritus	
Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting foetus [2*] Uterine contractions abnormal, uterine tachysystole, uterine hyperstimulation, uterine hypertonus Meconium in amniotic fluid	Postpartum haemorrhage, Premature separation of placenta, Apgar score low Arrested labour Chorioamnionitis Uterine atony	Anaphylactoid syndrome of pregnancy Fetal distress syndrome [3*] Fetal death, stillbirth, neonatal death [4*]
Reproductive system and breast disorders		Vulvovaginal burning sensation	Genital oedema
General disorders and administration site conditions		Febrile disorders	
Injury, poisoning and procedural complications			Uterine rupture

[1*] "Fetal heart rate disorder" was in clinical studies reported as "fetal heart rate abnormalities", "fetal bradycardia", "fetal tachycardia", "unexplained absence of normal variability", "fetal heart rate decreased", "fetal heart rate deceleration", "early or late decelerations", "variable decelerations", "prolonged decelerations".

[2*] "Abnormal labour affecting foetus" as expression for hyperstimulation syndrome was in clinical studies reported as "uterine tachysystole" combined with "late decelerations", "fetal bradycardia", or "prolonged decelerations".

[3*] "Fetal distress syndrome" was also reported as "fetal acidosis", "pathological CTG", "fetal heart rate abnormalities", "intrauterine hypoxia" or "threatening asphyxia". The term itself is unspecific, has a low positive predictive value and is often associated with an infant who is in good condition at birth.

[4*] 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, 4.3 and 4.4).

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 or hypersensitivity may lead to hyperstimulation of the uterine muscle with or without fetal distress. If fetal distress occurs, remove PROPESS immediately and manage in accordance with local protocol.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: uterotonics, prostaglandins

ATC-code: G02AD02

Prostaglandin E_2 (PGE_2) is a naturally occurring compound found in low concentrations in most tissues of the body. It functions as a local hormone.

Prostaglandin E_2 plays an important role in the complex set of biochemical and structural alterations involved in cervical ripening. Cervical ripening involves a transformation of the uterine cervix which must be transformed from a rigid structure to a soft, dilated configuration to allow passage of the fetus through the birth canal. This process involves activation of the enzyme collagenase which is responsible for the breakdown of the collagen.

Local administration of dinoprostone to the cervix results in cervical ripening which then induces the subsequent events which complete labour.

5.2 Pharmacokinetic properties

PGE_2 is rapidly metabolised primarily in the tissue of synthesis. Any which escapes local inactivation is rapidly cleared from the circulation with a half-life generally estimated as 1-3 minutes.

No correlation could be established between PGE_2 release and plasma concentrations of its metabolite, PGE_m. The relative contributions of endogenously and exogenously released PGE_2 to the plasma levels of the metabolite PGE_m could not be determined.

The reservoir of 10 mg dinoprostone serves to maintain a controlled and constant release. The release rate is approximately 0.3 mg per hour over 24 hours in women with intact membranes whereas release is higher and more variable in women with premature rupture of membranes. PROPESS releases dinoprostone to the cervical tissue continuously at a rate which allows cervical ripening to progress until complete, and with the facility to remove the dinoprostone source when the clinician decides that cervical ripening is complete or labour has started, at which point no further dinoprostone is required.

5.3 Preclinical safety data

Preclinical studies have demonstrated that dinoprostone is a locally acting substance which is rapidly inactivated and thus it has no significant systemic toxicity.

The hydrogel and polyester polymers are inert compounds with good local tolerability.

Reproduction toxicity, genotoxic or carcinogenic effects of the polymers have not been investigated but systemic exposure is negligible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrogel Polymer prepared with: Polyethylene Glycol 8000, Dicyclohexyl methane-4, 4'-diisocyanate, 1,2,6-Hexanetriol, Ferric chloride.

Polyester Retrieval System

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 freezer (-15^{0}C to -25^{0}C).

Store in the original container in order to protect from moisture. No thawing is required prior to use.

6.5 Nature and contents of container

Each vaginal delivery system is contained within an individual sealed foil sachet produced from an aluminium/polyethylene foil laminate strip and packed in a carton. Pack containing 5 vaginal delivery systems.

6.6 Special precautions for disposal and other handling

PROPESS should be removed from the freezer just prior to the insertion.

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

7. MARKETING AUTHORIZATION HOLDER

Ferring Pharmaceuticals Ltd, 8 Hashita St, IND. Park, Caesarea, 3088900, Israel

8. **MARKETING AUTHORIZATION NUMBER**
131-89-29517

9. **MANUFACTURER** Ferring Controlled Therapeutics Ltd (FCT), UK

This leaflet was revised in May 2024 according to MOH guidelines.