NAME OF THE MEDICINAL PRODUCT
CERVIDIL® 10 mg Vaginal Delivery System

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. It also contains crosslinked polyethylene glycol (hydrogel) and polyester yarn.

PHARMACEUTICAL FORM
Vaginal delivery system

CERVIDIL® is presented as a thin, flat semi-transparent polymeric vaginal delivery system which is rectangular in shape with rounded corners contained within a knitted polyester retrieval system.

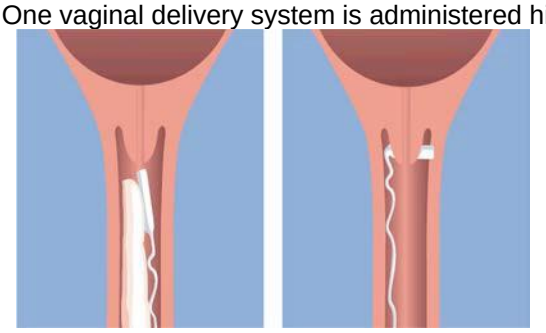
THERAPEUTIC INDICATIONS
Initiation of cervical ripening in patients, at or near term, who have favourable induction features and in whom there is a medical or obstetrical indication for induction of labour.

POSOLOGY AND METHOD OF ADMINISTRATION
CERVIDIL® should only be administered by qualified healthcare personnel in hospitals and clinics with 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.

In case of subsequent administration of uterotonic drugs, a dosing interval of at least 30 minutes is recommended following the removal of the vaginal delivery system.

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

Method of administration

Administration
CERVIDIL® 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 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 CERVIDIL®, 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 CERVIDIL® they will not reduce in frequency or intensity as long as CERVIDIL® remains in situ because dinoprostone is still being administered.
   (ii) Patients, particularly multigravidae, 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 CERVIDIL® 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 uterotonic drugs.

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 2-3 times its original size and be pliable.

CONTRAINDICATIONS

CERVIDIL® should not be used or left in place:

1. When labour has started.
2. When uterotonic 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 (see sections special warnings and precautions for use & undesirable effects)
   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.
6. When there is placenta previa or active herpes genitalis or unexplained vaginal bleeding during the current pregnancy.
7. When the patient is carrying more than one fetus or the fetus is in a non-vertex presentation.
8. When there is abnormal cardiotocography or suspected fetal compromise.
9. In the presence of any suggestion of uterine hyperstimulation or hypertonic uterine contractions.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The condition of the cervix should be assessed carefully before CERVIDIL® is used. After insertion, uterine activity and fetal condition must be monitored carefully and regularly by qualified healthcare personnel. CERVIDIL® must only be used in hospitals and clinics with 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 CERVIDIL®, mainly in patients with contra-indicated conditions (see section contraindications). Therefore, CERVIDIL® 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 CERVIDIL® is not recommended, as the effects of a second dose have not been studied.

CERVIDIL® should be used with caution in patients with a previous history of uterine hypertonus, glaucoma or asthma.

The experience of CERVIDIL® in patients with ruptured membranes is limited. Therefore, CERVIDIL® 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 undesirable effects). Therefore, 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).

CERVIDIL® should be used with caution when there is a multiple pregnancy. No studies in multiple pregnancy have been performed.

CERVIDIL® 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.

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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No dedicated interaction studies have been performed with CERVIDIL®.

Prostaglandins potentiate the uterotonic effect of uterotonic drugs. Therefore, CERVIDIL® should not be used concurrently with the use of uterotonic drugs.

Medication with non-steroidal anti-inflammatory drugs, including acetylsalicylic acid, should be stopped before administration of dinoprostone.

FETILITY, PREGNANCY AND LACTATION
Pregnancy
CERVIDIL® is for the initiation of cervical ripening in pregnant patients at term (from 37 completed weeks) only where labour induction is indicated.

CERVIDIL® is not indicated for use in 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 CERVIDIL®.

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 newborns have been observed in the clinical studies conducted.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Not relevant.

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 fetus” (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)	Frequency unknown
Blood and lymphatic system disorders			Disseminated intravascular coagulation
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 fetus[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 fetus" 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 posology and method administration, contraindications and special warnings and precautions for use).

OVERDOSE

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

PHARMACOLOGICAL PROPERTIES

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.

PGE_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.

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. CERVIDIL® 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.

LIST OF EXCIPIENTS
Crosslinked polyethylene glycol (hydrogel)
Polyester yarn

INCOMPATIBILITIES
Not applicable

SHELF LIFE
3 years

SPECIAL PRECAUTIONS FOR STORAGE
Store in a freezer between -10°C and -25°C. Store in the original container in order to protect from moisture.

The product can be stored in refrigerator (2 °C to 8°C) for a period not exceeding one month within the expiration date after taking out from the freezer.

NATURE AND CONTENTS OF CONTAINER
CERVIDIL® vaginal delivery systems are presented in individual, sealed aluminium/polyethylene laminate sachets in packs of 1 vaginal delivery system.

SPECIAL PRECAUTIONS FOR DISPOSAL
CERVIDIL® should be removed from the freezer just prior to the insertion.

After usage, the whole product should be disposed of as clinical waste.

MANUFACTURER
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G74 5PB Scotland United Kingdom

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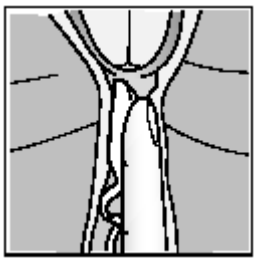
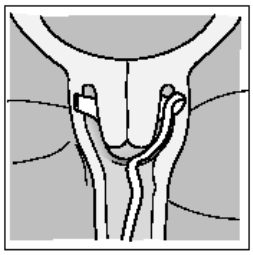
Issued to Medical Professionals Only
CERVIDIL®

INSTRUCTIONS

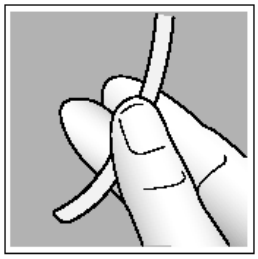
FOR USE



1) Holding the pessary between the fingers of the examining hand, insert CERVIDIL® high into the posterior vaginal fornix using only small amounts of water soluble lubricants.



2) To ensure that the pessary remains *in situ*, it should be turned through 90° so that it lies transversely in the posterior fornix.



3) Allow sufficient tape to remain outside the vagina to permit retrieval.

4) After insertion, ensure that the patient remains recumbent for 30 minutes.

RETRIEVAL INSTRUCTIONS

1) CERVIDIL® is removed quickly and easily by gentle traction on the retrieval tape.

2) CERVIDIL® should be removed immediately in the following circumstances:

   a) At the onset of labour.
   b) Spontaneous rupture of the membranes and at artificial rupture of the membranes.
   c) Any suggestion of uterine hyperstimulation or hypertonic uterine contractions.
   d) Evidence of fetal distress.
   e) Evidence of maternal systemic adverse dinoprostone effects such as nausea, vomiting, hypotension or tachycardia.
   f) At least 30 minutes prior to starting an intravenous infusion of oxytocin.

Manufactured by Ferring Controlled Therapeutics Limited, East Kilbride, G74 5PB, United Kingdom.