AUSTRALIAN PRODUCT INFORMATION - CERVIDIL® (DINOPROSTONE) (PROSTAGLANDIN E2) PESSARY SACHET

1. NAME OF THE MEDICINE

Dinoprostone (prostaglandin E2, PGE2)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pessary (vaginal insert) contains 10 mg of dinoprostone and releases a mean dose of approximately 0.3 mg per hour of dinoprostone over 24 hours. The dinoprostone is dispersed throughout a matrix consisting of 241 mg of hexanetriol/macrogol 8000/isocyanate cross-linked hydrogel copolymer, which is a semi-opaque, beige coloured, flat rectangular pessary (vaginal insert) measuring 29 mm by 9.5 mm and 0.8 mm in thickness.

3. PHARMACEUTICAL FORM

CERVIDIL is a thin, flat, polymeric pessary (vaginal insert) which is rectangular in shape with rounded corners. The pessary (vaginal insert) is contained within the pouch of an off white knitted polyester retrieval system designed to aid retrieval at the end of the dosing interval.

The pessary (vaginal insert) and its retrieval system, made of polyester yarn, are non-toxic and, when placed in a moist environment, absorb water, swell, and release dinoprostone.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Administration

CERVIDIL should be removed from the freezer immediately prior to the insertion. No thawing is required prior to use. To remove CERVIDIL from the packaging, first tear the foil along the tear mark across the top of the sachet. Do not use scissors or sharp instruments to cut the foil as this may damage the product. Use the retrieval tape to gently pull the product out of the sachet.

The pessary (vaginal insert) should be inserted immediately after removal from the freezer and its foil package, however, controlled periods of time of up to one month at 2-8°C can be allowed within the shelf life of the product. CERVIDIL must not be used without its retrieval system.

One pessary (vaginal insert) should be inserted high into the posterior vaginal fornix using only small amounts of water soluble lubricants to aid insertion (please refer to Figure 1). After CERVIDIL 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 PGE2 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 pessary (vaginal insert) can be removed quickly and easily by gentle traction on the retrieval tape. After removal, ensure that the entire product, pessary (vaginal insert) and retrieval system, has been removed from the vagina.

It is necessary to remove the pessary (vaginal insert) 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 PGE2 is still being administered, nor will they reduce if CERVIDIL is removed because the woman is in labour.
    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 pessary (vaginal insert) 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 PGE2 effects such as nausea, vomiting, hypotension or tachycardia.
6. At least 30 minutes prior to administration of other uterotonic medicines, e.g. oxytocin.
7. If there has been insufficient cervical ripening in 24 hours.

Upon removal of the product from the vagina, the pessary (vaginal insert) will have swollen to 2-3 times its original size and be pliable. The whole product should be disposed of as clinical waste.

4.3 CONTRAINDICATIONS

CERVIDIL SHOULD NOT BE USED OR LEFT IN PLACE IN THE FOLLOWING CONDITIONS:

1. When there is known hypersensitivity to dinoprostone or any other constituent of the pessary (vaginal insert) (e.g. urethane).
2. When the patient is carrying more than one fetus or the fetus is in a non-vertex presentation.
3. When labour has started.
4. When uterotonic medicines and/or other labour inducing agents are being given or if they are to be given intravenously within 30 minutes.

5. When strong prolonged uterine contractions would be inappropriate such as in patients:
    a. who have had previous major uterine surgery, e.g. caesarean section or myomectomy (see section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE AND section 4.8 - ADVERSE EFFECTS (UNDESIRABLE EFFECTS))
    b. who have had previous uterine cervix surgery or rupture of the cervix
    c. with cephalopelvic disproportion
    d. with fetal malpresentation
    e. with suspicion or evidence of fetal distress (e.g. abnormal cardiotocography).
6. When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted.
7. Where vaginal delivery is not indicated, e.g. placenta praevia or active herpes genitalis.
8. When there has been unexplained vaginal bleeding during the pregnancy.
9. When there is abnormal cardiotocography or suspected fetal compromise.
10. In the presence of any suggestion of uterine hyperstimulation or hypertonic uterine contractions.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For hospital use only

CERVIDIL should be administered only by trained obstetrical personnel in a hospital setting with appropriate obstetrical units with facilities for continuous fetal and uterine monitoring.

The condition of the cervix should be assessed carefully before CERVIDIL is used.
Use with caution in patients with cervical (Bishop) scores of 8 or more.

After insertion, uterine activity, fetal condition and the progression of cervical dilatation and effacement, must be monitored carefully and regularly by qualified healthcare personnel. If there is any suggestion of maternal or fetal complications, or if adverse effects occur, the pessary (vaginal insert) should be removed.

Uterine rupture has been reported in association with the use of CERVIDIL, mainly in patients with contraindicated conditions (see section 4.3 – 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 a possibility of uterine hypertonus or rupture and the vaginal insert should be removed immediately.

As with other uterotonic medicines, the possibility of uterine rupture should be considered in the presence of excessive uterine activity or unusual uterine pain.

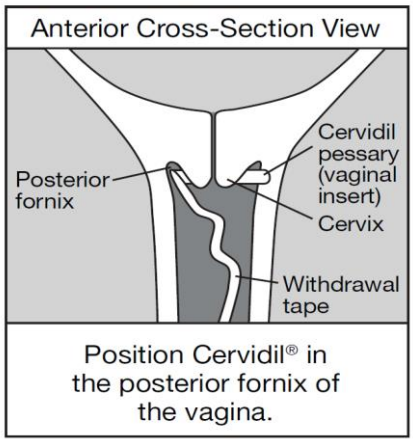
Prostaglandins potentiate the uterotonic effect of uterotonic medicines. CERVIDIL must be removed at least 30 minutes before administration of other uterotonic medicines (e.g. oxytocin) is initiated (see also section 4.5 – INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS), and the patient's uterine activity monitored carefully for uterine hyperstimulation.

If uterine hyperstimulation is encountered or if labour commences, the pessary (vaginal insert) should be removed immediately. CERVIDIL should also be removed prior to amniotomy.

A second dose of CERVIDIL is not recommended, as the effects of a second dose have not been studied.

After insertion, CERVIDIL should be positioned transversely into the posterior fornix of the vagina (Figure 1). Incorrect positioning of the pessary (vaginal insert) could lead to the loss of device from the vagina and consequent lack of efficacy due to insufficient exposure of the cervix to the appropriate sustained concentrations of prostaglandin.

Figure 1



CERVIDIL should be used with caution in patients with compromised cardiovascular function.

CERVIDIL should be used with caution in patients with a previous history of uterine hypertony, glaucoma, epilepsy 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.

CERVIDIL should be used with caution in patients who have had more than three full term deliveries.

Women aged 35 and over, women with complications during pregnancy, such as gestational diabetes, arterial hypotension and hypothyroidism, and women at gestational age above 40 weeks have a higher post-partum risk of developing disseminated intravascular coagulation (DIC). These factors may additionally enhance the risk of DIC in women with pharmacologically induced labour (see also section 4.8 - ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Therefore, dinoprostone should be used with caution in these women. In the immediate post-partum phase the physician should continue to monitor 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 embolisation of antigenic tissue causing, in rare circumstances, the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

Use in the elderly

No data available.

Paediatric use

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

Renal, pulmonary and hepatic impairment

The use of CERVIDIL in patients with diseases which could affect the metabolism or excretion of PGE2, e.g. liver, lung or kidney disease, has not been specifically studied. The use of CERVIDIL in such patients is not recommended.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No dedicated interaction studies have been performed with CERVIDIL.

Prostaglandins potentiate the uterotonic effect of uterotonic medicines. Concurrent use of CERVIDIL in patients receiving other uterotonic medicines is not recommended. A waiting period of at least 30 minutes is recommended before sequential use of other uterotonic medicines (e.g. oxytocin) following the removal of CERVIDIL (see also section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Medication with non-steroidal anti-inflammatory medicines, including aspirin, should be stopped before administration of CERVIDIL.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies have not been conducted with CERVIDIL.

Use in pregnancy (Category C)

Prostaglandin E2 has produced an increase in skeletal anomalies in rats and rabbits. No effect would be expected clinically, when used as indicated, since CERVIDIL is administered after the period of organogenesis. Prostaglandin E2 has been shown to be embryotoxic in rats and rabbits. Specific fetotoxicity studies of this dose form of PGE2 have not been conducted. However, an increase in still births was noted when PGE2 containing pessary (vaginal insert) were used in studies in pregnant rats. There has been idiosyncratic sensitivity of the uterus resulting in anoxia. Any dose that produces sustained increased uterine tone could put the embryo or fetus at risk.

CERVIDIL is for the initiation and/or continuation of cervical ripening in pregnant patients at term (from 37 completed weeks) only where labour induction is indicated. CERVIDIL is not indicated for use during early or other phases of pregnancy.

Use in lactation

CERVIDIL is not indicated for use during lactation.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of CERVIDIL on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

CERVIDIL is well tolerated.

Table 4 presents adverse events reported in the Phase 3 study (Miso-Obs-303) that compared MISODEL (misoprostol 200 micrograms vaginal insert) (n=678) to 10 mg dinoprostone vaginal insert (DVI) (n=680) in women at term or near-term gestation.

Table 1. A comparison of selected outcomes and adverse events of special interest from the Phase 3 pivotal study (Miso-Obs-303, The EXPEDITE study).

	CERVIDIL 10 mg (n=680)	**MISODEL 200 micrograms (n=678)**
Intrapartum Adverse Events		
Fetal heart rate disorder	177 (26.0)	176 (26.0)
Arrested labour	128 (18.8)	96 (14.2)
Meconium in amniotic fluid	92 (13.5)	120 (17.7)
Chorioamnionitis	59 (8.7)	38 (5.6)
Abnormal labour affecting fetus	19 (2.8)	70 (10.3)
Shoulder dystocia	19 (2.8)	8 (1.2)
Puerperal pyrexia	16 (2.4)	9 (1.3)
Uterine contractions abnormal	9 (1.3)	25 (3.7)
Postpartum Adverse Events		
Postpartum haemorrhage	40 (5.9)	42 (6.2)
Uterine atony	23 (3.4)	27 (4.0)
Endometritis	10 (1.5)	13 (1.9)
Hypertension	9 (1.3)	13 (1.9)
Perineal laceration	12 (1.8)	8 (1.2)
Puerperal pyrexia	7 (1.0)	13 (1.9)
Oedema peripheral	9 (1.3)	7 (1.0)
Neonatal Adverse Events		
Caput succedaneum	60 (8.8)	58 (8.6)
Infection prophylaxis	63 (9.3)	46 (6.8)
Neonatal respiratory depression	31 (4.6)	34 (5.0)
Hypoglycaemia neonatal	22 (3.2)	19 (2.8)
Cephalhaematoma	16 (2.4)	16 (2.4)

	CERVIDIL 10 mg (n=680)	MISODEL 200 micrograms (n=678)
Transient tachypnoea of the newborn	15 (2.2)	12 (1.8)
Apgar score low	7 (1.0)	13 (1.9)
Neonatal aspiration	9 (1.3)	8 (1.2)

Table 2. Adverse reactions in clinical studies presented by system organ classes (SOC) and frequency.

Preferred term	Common (≥ 1/100 and < 1/10)	Uncommon (≥ 1/1000 and < 1/100)
Nervous system disorders		Headache
Cardiac disorders	Fetal heart rate disorder[1]*	
Vascular disorders		Hypotension
Respiratory, thoracic and mediastinal disorders		Neonatal respiratory distress related conditions
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
Reproductive system and breast disorders		Vulvovaginal burning sensation
General disorders and administration site conditions		Febrile disorders

[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"

In study 101-801, five minute Apgar scores were below 7 in 1.8% (646/658) of studied neonates whose mothers received CERVIDIL for up to 12 hours. In Miso-Obs-303, where CERVIDIL was inserted up to 24 hours, five minute Apgar scores of below 7 were reported in neonates of 1% of participants.

In a report of a 3-year paediatric follow-up study in 121 infants, 51 of whose mothers received CERVIDIL for up to 12 hours, there were no deleterious effects on physical examination or psychomotor evaluation.

Post-marketing Experience

Table 3: Adverse reactions in post-authorisation reports presented by SOC and frequency unknown.

System organ class	Frequency unknown
Blood and lymphatic system disorders	Disseminated intravascular coagulation
Immune system disorders	Anaphylactic reaction Hypersensitivity
Gastrointestinal disorders	Abdominal pain Nausea Vomiting Diarrhoea
Pregnancy, puerperium and perinatal conditions	Anaphylactoid syndrome of pregnancy Fetal distress syndrome[1]* Fetal death, stillbirth, neonatal death[2*]
Reproductive system and breast disorders	Genital oedema
Injury, poisoning and procedural complications	Uterine rupture

[1]* "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.

[2*] 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).

An increased risk of post-partum DIC has been reported in patients whose labour was induced by pharmacological means, either with dinoprostone or oxytocin.

In post-marketing experience reports, uterine rupture has been reported in association with the use of CERVIDIL.

Influence of Removal of CERVIDIL on Adverse Events

In study 101-801 (with the retrieval system) cases of hyperstimulation reversed within 2 to 13 minutes of removal of the product. Tocolytics were required in one of the five cases.

In cases of fetal distress, when product removal was thought advisable, there was a return to normal rhythm and no neonatal sequelae.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

CERVIDIL is used as a single dosage in a single application. Overdosage is usually manifested by uterine hyperstimulation which may or may not be accompanied by fetal distress. If fetal distress occurs, remove the pessary (vaginal insert) immediately and

manage in accordance with local protocol. Other treatment must be symptomatic since, to date, clinical experience with prostaglandin antagonists is insufficient.

The use of beta-adrenergic agents should be considered in the event of undesirable increased uterine activity, if removal does not diminish the undesirable uterine activity.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

PGE2 is a naturally occurring compound found in low concentrations in most tissues of the body. It functions as a local hormone.

PGE2 plays an important role in the complex set of biochemical and structural alterations involved in cervical ripening. Cervical ripening involves a marked relaxation of the cervical smooth muscle fibres of the uterine cervix which must be transformed from a rigid structure to a softened, yielding and dilated configuration to allow passage of the fetus through the birth canal. This process involves activation of the enzyme collagenase which is responsible for digestion of some of the structural collagen network of the cervix.

Clinical trials

Trials involving insertion of CERVIDIL for up to 12 hours

Three randomised, double-blind, placebo-controlled studies have been conducted in which CERVIDIL was inserted for up to 12 hours. If successful, cervical ripening was achieved at the end of the 12-hour period, amniotomy was performed (if necessary) and oxytocin infusion commenced (if necessary, after waiting at least 30 minutes from removal of the pessary). Studies 101-003 and 101-103 involved the pessary (vaginal insert) alone, whereas study 101-801 used the pessary (vaginal insert) fitted with retrieval system to facilitate rapid and reliable retrieval of the pessary (vaginal insert). Pharmacokinetic studies had demonstrated that there was no significant difference between the PGE2 release characteristics of the "netted" and “unnetted" versions of the pessary (vaginal insert).

All three studies involved patients with singleton pregnancies and cephalic presentation, for whom there were medical or obstetrical grounds for the induction of labour, and who had a Bishop score of 4 or less. Patients had to be in at least the 37th week of gestation. On randomisation, patients were stratified according to whether they were primiparous or multiparous.

The efficacy of CERVIDIL as demonstrated in these studies is shown in Table 4.

Table 4. Efficacy of CERVIDIL in Double Blind Studies.

		Primip/Nulliparous		Multiparous		
Parameter	**Study**	**CERVIDIL**	**Placebo**	**CERVIDIL**	**Placebo**	**P-Value**
Treatment Success*	101-103 (n=81)	65%	28%	87%	29%	<0.001
	101-003 (n=371)	68%	24%	77%	24%	<0.001
	101-801 (n=206)	72%	48%	55%	41%	0.003
Time to Delivery (hrs)						
Average	101-103 (n=81)	33.7	48.6	14.0	28.6	
Median		25.7	34.5	12.3	24.6	0.001
Average	101-801 (n=206)	31.1	51.8	52.3	45.9	
Median		25.5	37.2	20.8	27.4	<0.001
Time to Onset of Labour (hrs)						
Average	101-103 (n=81)	19.9	39.4	6.8	22.4	
Median		12.0	19.2	6.9	18.3	<0.001

*Treatment success was defined as Bishop score increase at 12 hours of ≥3, vaginal delivery within 12 hours or Bishop score at 12 hours > 6. These studies were not designed with the power to show differences in caesarean section rates between CERVIDIL and placebo groups and none were noted.

Trials involving insertion of CERVIDIL for up to 24 hours

Miso-Obs-004 and Miso-Obs-303

The efficacy of the CERVIDIL pessary (vaginal insert) in cervical ripening when insertion for up to 24 hours was permitted has been studied in two Phase 3 trials: Miso-Obs-303 and Miso-Obs-004. Both studies were double-blind, randomised, active-controlled trials in pregnant subjects requiring cervical ripening and induction of labour, where CERVIDIL dinoprostone vaginal insert (DVI) was used as an active comparator for misoprostol vaginal insert 200 micrograms (MVI 200) [Miso-Obs-303], 100 micrograms (MVI 100) or 50 micrograms (MVI 50) [Miso-Obs-004]. Intravenous oxytocin was permitted, when required, 30 minutes following removal of the study drug assuming no contraindications and active labour not present.

The primary efficacy endpoint of Miso-Obs-004 and Miso-Obs-303 was time to vaginal delivery.

The secondary efficacy endpoints of Miso-Obs-004 were cervical ripening based on success on the composite modified Bishop score at 12 hours: proportion of vaginal deliveries within 12 and 24 hours; need for oxytocin in the first and/or second stages of labour; and time to onset of active labour in the first and/or second stages of labour.

The secondary efficacy endpoints of Miso-Obs-303 were time to any delivery (vaginal or caesarean); time to active labour; proportion of subjects with pre-delivery oxytocin; proportion of subjects with vaginal delivery within 12 hours; proportion of subjects with any delivery within 24 hours; proportion of subjects with any delivery within 12 hours; proportion of subjects with vaginal delivery within 24 hours; proportion of subjects with vaginal delivery; and proportion of subjects with cervical ripening success at 12 hours.

MISODEL (MVI 200), but not MVI 100 or MVI 50, is registered in Australia for induction of labour in women with an unfavourable cervix, from 36 weeks' gestation in whom induction is clinically indicated and in a hospital where continuous electronic fetal monitoring is available.

An overview of these trials is presented in Table 5.

Table 5. Overview of Clinical Trials Contributing to Efficacy Data.

Trial ID	Design	Treatments	Number of Subjects	Population
Miso-Obs-303	Double-blind, randomised, active-controlled	DVI: 10 milligrams MVI: 200 micrograms	DVI: 680 MVI 200: 678	Pregnant women at ≥ 36 weeks 0 days gestation, parity ≤ 3 and baseline mBS ≤ 4
Miso-Obs-004	Double-blind, randomised, active-controlled	DVI: 10 milligrams MVI: 100 micrograms MVI: 50 micrograms	DVI: 436 MVI 100: 428 MVI 50: 443*	Pregnant women at ≥ 36 weeks 0 days gestation, parity ≤ 3 and baseline mBS ≤ 4

* One additional subject signed a consent form that had expired thus no trial information was reported.

DVI=Dinoprostone vaginal insert; mBS= modified Bishop Score; MVI=Misoprostol vaginal insert

Approximately 60% of the women in these two Phase 3 trials required cervical ripening to continue beyond 12 hours and a total of 302 women had the insert in situ for 24 hours during the two trials (83 in Miso-Obs-004 and 219 in Miso-Obs-303). Table 3 shows the efficacy results in both trials, where results for the DVI group are consistent in these two Phase 3 trials.

Table 6. Comparison of Efficacy Results in Miso-Obs-303 and Miso-Obs-004 (ITT Population).

Endpoints	Miso-Obs-303		Miso-Obs-004		
	DVI (N=680)	MVI 200 (N=678)	DVI (N=436)	MVI 100 (N=428)	MVI 50 (N=443)
Subjects with composite endpoint of cervical ripening at 12 h, n (%)	449 (66.0)	551 (81.3)	260 (59.6)	254 (59.3)	223 (50.3)
Median time to active labour during first hospitalisation (h)	18.6	12.1	15.4	15.4	22.3
Subjects who received pre-delivery oxytocin during first hospitalisation, n (%)	497 (74.1)	324 (48.1)	301 (69.0)	293 (68.5)	358 (80.8)
Subjects with vaginal delivery within 12 h, n (%)[1]	57 (8.38)	134 (19.76)	51 (11.7)	36 (8.4)	23 (5.20)
Subjects with vaginal delivery within 24 h, n (%)[1]	231 (33.97)	370 (54.57)	186 (42.7)	185 (43.2)	128 (28.9)
Median time to vaginal delivery during first hospitalisation (h)	32.8	21.5	27.5	26.6	35.5
Rate of caesarean delivery during first hospitalisation n, (%)	184 (27.06)	176 (25.96)	115 (26.4)	119 (27.8)	124 (28.0)
Median time to any delivery (vaginal or caesarean) during first hospitalisation (h)	27.3	18.3	23.4	22.4	29.2

[1] Percentage for this endpoint are based on all ITT subjects for consistency of data presentation between trials.

DVI=Dinoprostone vaginal insert; ITT=Intent to treat; MVI=Misoprostol vaginal insert; n=Number of subjects.

A total of 8.38% and 11.7% of subjects in the DVI groups delivered vaginally within 12 hours which increased to 33.97% and 42.7% by 24 hours in the Miso-Obs-303 and Miso-Obs-004 trials, respectively. There were 66.0% and 59.6% of subjects in the DVI groups who achieved the composite endpoint for cervical ripening at 12 hours in Miso-Obs-303 and Miso-Obs-004 trials, respectively. In Miso-Obs-303, the percentage of subjects in the DVI group with cervical ripening success increased to 86.8% at 24 hours.

5.2 PHARMACOKINETIC PROPERTIES

CERVIDIL releases PGE2 to the cervical tissue continuously at a rate which allows cervical ripening to progress until complete (mean dose of approximately 0.3 mg per hour over 24 hours), and with the facility to remove the PGE2 source when the clinician decides that no further PGE2 is required.

Dinoprostone is established as a successful agent for cervical ripening and induction of labour. Dinoprostone initiates labour by a process which may be more akin to spontaneous labour than that produced by forewater amniotomy followed by oxytocin infusion. Local application of dinoprostone (endocervical and vaginal) has proved to be clinically superior to intravenous administration, avoiding gastrointestinal side effects.

Distribution

Using equilibrium dialysis, studies indicate that dinoprostone is approximately 73% bound to human plasma albumin.

Metabolism

Dinoprostone is rapidly metabolised in the lungs, kidneys and liver. Approximately 90% of dinoprostone is metabolised in the first pass. In man, three metabolites of dinoprostone have been identified in plasma, 13,14-dihydro-15-keto GE_2 (the primary metabolite), 11 alpha-hydroxy-9,15-diketoprost-5-enoic acid and 11 alpha-hydroxy-9,15-dioxyprost-5-13-dienoic acid.

Excretion

Dinoprostone is eliminated from the circulation very rapidly. Studies indicate that the half-life of dinoprostone is less than one minute.

The plasma concentration of dinoprostone and its metabolites is low after intravaginally administered PGE2. The plasma half-life for dinoprostone is less than 1 minute and for its primary metabolite less than 10 minutes. Animal studies have shown that this metabolite (15-keto-13,14-dihydro-PGE2) is about half as active as the mother substance. Dinoprostone is metabolised in the lung and is excreted via the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence of mutagenicity has been observed with PGE2 in the Micronucleus Test, or Ames Test. PGE2 did induce chromosomal aberrations in Chinese hamster lung fibroblasts in culture but only at an unphysiologically high concentration.

Long term clinical use of chemically related polymers such as those used in the hydrogel and retrieval system has not identified any concerns regarding genotoxicity.

Carcinogenicity

Long-term carcinogenicity studies have not been conducted with CERVIDIL.

Exposure to PGE2 at the dosage and administration recommended for induction of labour is not considered to be of concern with regard to potential carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to **section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION**

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a freezer below -18°C. The pessary (vaginal insert) should be inserted immediately after removal from the freezer and its foil package, however, controlled periods of time of up to one month at 2 to 8°C can be allowed within the shelf life of the product.

Pessaries (vaginal inserts) exposed to high humidity will absorb moisture from the air and thereby alter the release characteristics of dinoprostone. Once used, the pessary (vaginal insert) should be discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

CERVIDIL is presented in an individual, sealed aluminium/polyethylene laminate sachet containing 1 pessary (vaginal insert).

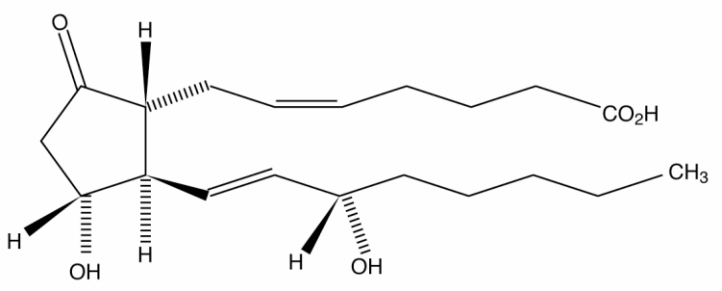
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical Structure

The structural formula is represented below:



Molecular formula: $C_{20}H_{32}O_5$ Molecular weight: 352.5

CAS number
363-24-6

The chemical name for dinoprostone (commonly known as prostaglandin E2 or PGE2) is 11alpha-5Sdihydroxy-9-oxo-prosta-5Z,13E-dien-1-oic acid. It is a white to off-white crystalline powder. It has a melting point within the range of 65°C to 69°C. Dinoprostone is soluble in ethanol and in 25% ethanol in water.

7. MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8. SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

Toll Free: 1800 337 746
www.ferring.com.au

9. DATE OF FIRST APPROVAL

12 December 2001

10. DATE OF REVISION

9 May 2022

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/ or http://www.ferring.com.au/

Summary table of changes

Section Changed	Summary of new information
4.4	Strengthening of warnings and precautions related to uterine hyperstimulation and patient monitoring
4.8	Addition of post-marketing adverse drug reactions
Multiple sections	Change references to ‘oxytocin’ and ‘oxytocics’ to ‘uterotonic medicines’. Editorial changes and corrections.