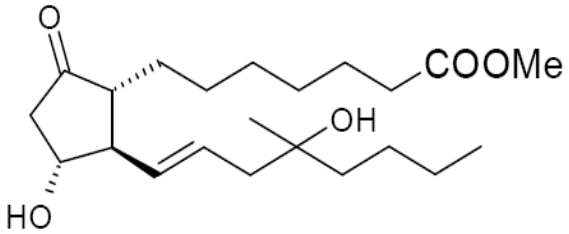
NAME OF THE MEDICINE

MISODEL® Modified-Release Pessary (vaginal insert)
misoprostol 200 micrograms

The chemical name for misoprostol (a synthetic analogue of prostaglandin E_1 or PGE_1) is (±)-(11a, 13E)-11, 16-dihydroxy-16-methyl-9-oxo-prost-13-en-1-oic acid-methyl ester.

The structural formula (relative stereochemistry) is:



Active

Molecular formula: $C_{22}H_{38}O_5$
Molecular weight: 382.53
CAS No. 59122-46-2

DESCRIPTION

MISODEL is a modified-release pessary (vaginal insert). Each vaginal insert consists of 200 micrograms misoprostol dispersed in a dose reservoir of 241 mg hexanetriol/macrogol 8000/isocyanate cross-linked hydrogel copolymer vaginal insert contained in a polyester retrieval system (inert woven polyester pouch and tail). The hydrogel copolymer contains 0.13 mg of butylated hydroxyanisole as an antioxidant.

MISODEL vaginal insert is a controlled release formulation that swells in the presence of moisture, causing drug release to occur.

Misoprostol is released *in vivo* at a mean rate of approximately 7 micrograms/hour over a period of 24 hours. Drug release continues as long as MISODEL is in the vagina.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Other gynaecologicals, oxytocics, prostaglandins, ATC-code: G02AD06.

Misoprostol is a synthetic analogue of Prostaglandin E_1 (PGE_1), a naturally occurring oxytocic compound. Prostaglandins of the F and E series have been shown to increase collagenase activity in rabbit uterine cervix fibroblasts *in vitro* and to cause cervical ripening and uterine contraction *in vivo*. These pharmacodynamic effects are considered to be the mechanism of action relevant for the clinical effect of MISODEL.

PGE analogues also have a number of other effects, e.g. relaxation of bronchial and tracheal muscles, increase of mucus secretion and decrease of acid and pepsin secretion in the stomach, increase of renal blood flow, increase of circulating concentrations of adrenocorticotropic hormone and prolactin. These pharmacodynamic effects are considered to be of no clinical importance with short-term treatment.

Pharmacokinetics

Absorption

In non-pregnant women, the MISODEL vaginal insert has a controlled mean *in vivo* release rate of approximately 7 micrograms/hour over a period of 24 hours. In a study of 24 pregnant women at term gestation, a median C_{max} of 45.8 pg/mL with a median T_{max} of 4 hours was observed. Median terminal half-life (after removal of the insert) was approximately 40 minutes. The serum protein binding of

misoprostol acid is less than 90% and concentration independent at therapeutic doses.

Distribution
The serum binding of misoprostol is not extensive (less than 90%) and is concentration independent in the therapeutic range. Misoprostol does not accumulate in red blood cells.

Metabolism
Misoprostol, an ester, is rapidly metabolised to its active metabolite misoprostol acid. Only misoprostol acid is detectable in plasma.

Excretion
The acid is further metabolised to inactive dinor and tetranor acid metabolites prior to excretion in the urine.

CLINICAL TRIALS

The phase-3 pivotal study, (Miso-Obs-303: The EXPEDITE study), was a double-blind, randomised, multicentre study conducted in the US with 1,358 pregnant women. The pregnant women were at or near term gestation and required cervical ripening and induction of labour. The study compared the efficacy and safety of MISODEL to 10 mg dinoprostone vaginal insert (DVI). Nulliparous and parous women aged ≥ 18 years at ≥ 36 weeks gestation with an unfavourable cervix (modified Bishop score ≤ 4) were randomly assigned to receive MISODEL or 10 mg dinoprostone vaginal insert (DVI) for up to 24 hours treatment. The co-primary efficacy endpoint of the study was time to vaginal delivery and the co-primary safety endpoint was the incidence of Caesarean deliveries. The results for key efficacy endpoints are shown in Table 1.

Table 1: Miso-Obs-303: The EXPEDITE study key efficacy endpoint results.

	MISODEL 200 micrograms (N=678)	**DVI[#] 10 mg (N=680)**	**p-value**
Median time to vaginal delivery of neonate (hours)[*]	21.5h[**]	32.8h[**]	p < 0.001
Nulliparous subjects	29.2 h (n=441)	43.1 h (n=451)	p < 0.001
Parous subjects	13.4 h (n=237)	20.1 h (n=229)	p < 0.001
Median time to overall delivery of the neonate[*] (vaginal and caesarean) (h)	18.3h[†]	27.3h[†]	p < 0.001
Overall median time to onset of active labour (hours)[*]	12.1h[††]	18.6h[††]	p < 0.001
Overall number of subjects who received pre-delivery oxytocin [n (%)]	324 (48.1%) (N=674)	497 (74.1%) (N=671)	p < 0.001

[#]*DVI = 10 mg dinoprostone vaginal insert*

[*] *Subjects who had a Caesarean delivery, were discharged prior to delivery or withdrew consent during the first hospitalisation were censored using the longest time interval from study drug administration to Caesarean delivery or to labour and delivery discharge (Kaplan Meier estimates).*

[**] *Summary of median time to vaginal delivery (only subjects who delivered vaginally): MISODEL, 200 micrograms: 16.6 h; 10 mg dinoprostone vaginal insert (DVI): 25.1 h,*

[†] *Summary of median time to any delivery: MISODEL, 200 micrograms: 18.2 h; 10 mg dinoprostone vaginal insert (DVI): 27.2 h ,*

[††] *Summary of median time to onset of active labour: MISODEL, 200 micrograms: 12.0 h; 10 mg dinoprostone vaginal insert (DVI): 18.0 h*

The results for Caesarean delivery endpoints are shown in Table 2.

Table 2: Rates of Caesarean delivery in the overall, nulliparous and parous populations of Miso-Obs-303 (The EXPEDITE Study).

	MISODEL	**DVI[#]**	**Treatment difference [Percentage Points (95% CI)]**
All parity	176/678 (26.0%)	184/680 (27.1%)	-1.10 (-5.79, 3.59)
Nulliparous	152/441 (34.5%)	168/451 (37.3%)	-2.78 (-9.08, 3.51)
Parous	24/237 (10.1%)	16/229 (7.0%)	3.14 (-1.93, 8.20)

[#]*DVI = 10 mg dinoprostone vaginal insert*

The non-inferiority margin for Caesarean delivery rate was pre-specified as 10% relative to the rate for 10 mg dinoprostone vaginal insert (DVI) (e.g for the all-parity group the delivery rate following DVI was 27.1% and the non-inferiority margin is therefore 2.71% percentage points). For the all-parity group (ITT population), the upper limit of the 95% CI for the difference in delivery rates between treatments was 3.6 percentage points (exceeding the non-inferiority margin of 2.71 percentage points), therefore non-inferiority was not met. Non-inferiority was met for the nulliparous group, but not the parous group; these results are difficult to interpret because of the problem of statistical multiplicity.

Compared to the 10 mg dinoprostone vaginal insert (DVI), MISODEL reduces the time to delivery, but also increases the risk of uterine tachysystole and foetal adverse events. A comparison between the study groups of adverse events of special interest from Miso-Obs-303 is provided in Table 3, located under **ADVERSE EFFECTS.**

INDICATIONS

MISODEL is indicated for the induction of labour in women with an unfavourable cervix, from 36 weeks gestation:

- in whom induction is clinically indicated
- in a hospital where continuous electronic foetal monitoring is available.

CONTRAINDICATIONS

MISODEL is contraindicated:

- When labour has started
- In hospitals where it is not possible to institute continuous electronic foetal heart monitoring
- When there is suspicion or evidence of foetal compromise before induction (e.g., failed non-stress or stress test, meconium staining or diagnosis or history of non-reassuring foetal status)
- When the patient is already receiving oxytocic drugs or other labour induction agents
- When there is suspicion or evidence of uterine scar resulting from previous uterine or cervical surgery (e.g. Caesarean section)
- When there is uterine abnormality (e.g. bicornate uterus)
- When there is placenta praevia or unexplained vaginal bleeding after 24 weeks gestation with this pregnancy
- When there is foetal malpresentation
- When there are signs or symptoms of chorioamnionitis, unless adequate prior treatment has been instituted
- Foetal macrosomia
- Oligohydramnios
- Multiple foetuses
- In women who have had more than 3 previous vaginal deliveries after 24 weeks gestation. MISODEL has not been studied in women who have had more than three previous vaginal deliveries after 24 weeks gestation.
- Before 36 completed weeks gestation
- Where there is hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

MISODEL is only for use in hospitals with the capability to continuously monitor foetal heart rate and uterine contractions. Prescribers should ensure that their hospital has a protocol in place to minimise the risk to the mother and foetus. Elements of the protocol should include:

- Guidance that MISODEL should only be used for low-risk pregnancies after 36 weeks gestation
- Clear guidance about what constitutes a low-risk pregnancy (see CONTRAINDICATIONS)
- Guidance on the requirements for continuous foetal heart rate and uterine contractility monitoring
- Hospital-specific audits of the outcomes for women receiving MISODEL versus other methods of induction of labour.

The risk of rare serious outcomes in the mother (e.g., amniotic fluid embolism, uterine rupture) or baby (encephalopathy, stillbirth, neonatal death) with MISODEL is unknown. Clinical trials of MISODEL and misoprostol tablets (vaginally, off-label) are not large enough either alone or pooled to quantify the risk of these serious outcomes (e.g., amniotic fluid embolism, uterine rupture, encephalopathy, stillbirth, neonatal death).

In a high-quality randomised trial (Obs-Miso-303) involving as a comparator 10 mg dinoprostone vaginal insert (DVI), MISODEL resulted in about three times more uterine tachysystole reported as an adverse event (13.3% versus 4.0%), four times more uterine tachysystole associated with non-reassuring foetal heart rate patterns (10.3% versus 2.6%), and required three times more tocolysis use (12.2% versus 4.1%). Preparedness for tocolytic therapy when MISODEL is used is therefore recommended. MISODEL can cause excessive uterine stimulation if left in place after onset of active labour (see Overdosage).

If uterine contractions are prolonged or excessive, or there is a clinical concern for the mother or baby, remove the vaginal delivery system. If excessive uterine contractions continue after drug removal, tocolytic treatments should be considered.

In women with pre-eclampsia, evidence or suspicion of foetal compromise should be ruled out (see Contraindications). Pregnant women with severe pre-eclampsia marked by Haemolytic anaemia; Elevated Liver enzymes; Low Platelet count (HELLP) syndrome, other end organ affliction or CNS findings other than mild headache were not studied in the pivotal Phase-3 trial (Miso-Obs-303; The EXPEDITE Study).

MISODEL has not been studied in women whose membranes have been ruptured for more than 48 hours prior to the insertion of MISODEL.

For women with positive Group B Streptococcus status requiring prophylactic antibiotics, careful consideration should be given regarding timing of antibiotic therapy in order to achieve adequate protection. In the pivotal Phase-3 study (Miso-Obs-303; The EXPEDITE Study), the shortest observed time to any delivery was 2.95 hours.

Remove MISODEL before oxytocin administration is initiated. Wait at least 30 minutes after removing MISODEL before initiating oxytocin (see Dosage and Administration, Contraindications and Interactions). MISODEL has only been studied in singleton pregnancies with cephalic presentation. No studies in multiple pregnancies have been performed.

MISODEL should only be used when induction of labour is clinically indicated.

MISODEL should be used with caution in patients with modified bishop score (mBS) >4.

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

An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour has been induced by any physiological or pharmacological method.

Butylated hydroxyanisole is used as an antioxidant in the cross-linked hydrogel polymer. It is only present in trace amounts in the final drug product. Butylated hydroxyanisole can cause skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Effects on fertility
In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation loss was observed with misoprostol at oral doses ≥ 1 mg/kg/day (estimated to yield 23 times the plasma AUC for misoprostol acid in patients at the recommended dose). Post-implantation loss was also increased with oral administration at 10 mg/kg/day. The no observed adverse effect level was 0.4 mg/kg/day.

Use in Pregnancy
MISODEL has been studied in pregnant women ≥ 36 weeks gestation. MISODEL should not be used prior to 36 weeks of gestation.

Use of misoprostol in early gestation has been associated with birth defects in humans. Reproductive toxicity studies in animals showed embryotoxicity (increased resorptions) with oral doses of 1 mg/kg/day in rabbits, 10 mg/kg/day in rats and 20 mg/kg in mice when treatment occurred during the period of organogenesis. An increased incidence of skeletal abnormalities was observed with an oral dose of 1 mg/kg/day in rabbits (possibly due to maternal toxicity) while an increased incidence of cleft palate was seen at a single oral dose of 30 mg/kg in mice. Studies in rats involving administration of misoprostol at later stages of pregnancy identified no adverse effects on pre-/postnatal development at an oral dose of 1 mg/kg/day given from late gestation and during lactation, and no effect on litter viability with single intravaginal administration in late gestation at a dose of 82 micrograms per kg. Systemic exposure to misoprostol acid in rats at these doses was 23–29 times higher than in patients treated with MISODEL.

Use in Lactation
No studies have been performed to investigate the amount of misoprostol acid in colostrum or breast milk following the use of MISODEL.

Misoprostol acid has been detected in human milk following oral administration of misoprostol in tablet form.

After removal of MISODEL, the median half-life in plasma of misoprostol acid is approximately 40 minutes. After five half-lives, i.e. approximately 3 hours, the misoprostol acid levels in the maternal plasma are negligible. Misoprostol acid may be excreted in colostrum and breast milk, but the level and duration is expected to be very limited and should not hinder breast-feeding.

With MISODEL no effects on the breastfed newborns have been observed in the clinical development programme.

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

Use in Elderly
MISODEL is not intended for use in the elderly.

Use in special populations
No studies in special populations have been conducted because the target population is pregnant women, and the dosing schedule is a single dose for no more than 24 hours.

Genotoxicity
Misoprostol has been evaluated in tests for mutagenicity in bacterial, yeast and mammalian cells, and for clastogenicity *in vitro* (Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). No evidence of genotoxicity was observed.

Carcinogenicity
Carcinogenicity studies by the intravaginal route have not been conducted for MISODEL. Oral administration of misoprostol at doses up to 2.4 mg/kg/day for 24 months in rats and up to 16 mg/kg/day for 21 months in mice did not increase tumour incidence in either species. These doses are more than 100 times the recommended human dose of misoprostol with use of MISODEL, based on mg/m^2 body surface area.

Interaction with other medicines

No interaction studies have been performed with MISODEL.

Concurrent use of oxytocic drugs or other labour induction agents is contraindicated due to the potential of increased uterotonic effects (see Contraindications).

Other prostaglandin-containing products were given to subjects if needed in the clinical trials following removal of MISODEL without apparent ill effect. A one-hour waiting period following removal of MISODEL was utilised prior to allowing these products.

ADVERSE EFFECTS

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

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

	MISODEL 200 micrograms (n=678) No (%)	**DVI[#] 10 mg (n=680) No (%)**	**RR (95%CI)**
Uterine tachysystole (AE)	90 (13.3%)	27 (4.0%)	3.34 (2.20, 5.07)
With foetal heart rate involvement (late decelerations, prolonged decelerations, bradycardia)	70 (10.3%)	18 (2.6%)	3.90 (2.35, 6.48)
Tocolysis use	83 (12.2%)	28 (4.1%)	2.97 (1.96, 4.50)
Meconium in amniotic fluid	120 (17.7%)	92 (13.5%)	1.31 (1.02, 1.68)
5 min Apgar <7	14 (2.1%)	7 (1.0%)	2.01 (0.81, 4.94)
Foetal acidosis	8 (1.2%)	4 (0.6%)	2.01 (0.61, 6.63)
Neonatal encephalopathy	4 (0.6%)	1 (0.1%)	4.01 (0.45, 35.80)

[#]*DVI = 10 mg dinoprostone vaginal insert*

The adverse reaction profile in Table 4 is based upon five clinical studies conducted with MISODEL in 874 pregnant women at term gestation. The most common adverse reactions are uterine contractions abnormal, foetal heart rate disorder and abnormal labour affecting foetus. Table 4 includes adverse reactions from Studies Miso-Obs-002, Miso-Obs-003, Miso-Obs-204, Miso-Obs-205 and Miso-Obs-303 (The EXPEDITE Study).

Table 4: Adverse Reactions observed in Clinical Studies

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Cardiac disorders	Foetal heart rate disorder[†]	
Gastrointestinal disorders		Nausea, Vomiting
Injury, poisoning and procedural complications		Uterine rupture
Investigations		Apgar score low*, Blood pressure increased
Nervous system disorders		Hypoxic-ischaemic encephalopathy*
Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting foetus[††], Meconium in amniotic fluid, Uterine contractions abnormal[†††]	Antepartum haemorrhage, Foetal acidosis*, Postpartum haemorrhage, Premature separation of placenta, Uterine hypertonus
Respiratory, thoracic and mediastinal disorders		Neonatal respiratory depression*, Neonatal respiratory distress syndrome*, Transient tachypnoea of the newborn*
Skin and subcutaneous tissue disorders		Pruritus general, Rash

** Neonatal adverse reactions. [†]Foetal heart rate disorder was reported as foetal heart rate abnormalities, foetal bradycardia, foetal, tachycardia, unexplained absence of normal variability, foetal heart rate decreased, foetal heart rate deceleration, early or late decelerations, variable decelerations, and prolonged decelerations. [††]Abnormal labour affecting fetus was reported as uterine tachysystole or uterine hypertonus with foetal heart rate disorder. [†††]Uterine contractions abnormal were reported as uterine tachysystole.*

In the pivotal MISODEL study (Miso-Obs-303: The EXPEDITE Study), the subjects were asked to report any hospital admission or emergency room visits on behalf of the neonate during the first month after delivery. No neonatal adverse reactions were reported following hospital discharge. There are no data on long-term outcomes for the baby following use of MISODEL.

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 via the Australian Adverse Drug Reaction Reporting System.

DOSAGE AND ADMINISTRATION

Dosage

MISODEL is a controlled release vaginal insert containing 200 micrograms of misoprostol which is released at a mean rate of approximately 7 micrograms/hour over a period of 24 hours.
The maximum recommended dose is one MISODEL vaginal insert (200 micrograms).

Remove MISODEL

- at the onset of active labour
- if uterine contractions are prolonged or excessive
- if there is evidence of foetal compromise or
- if 24 hours have elapsed since insertion.

If MISODEL falls out, do not replace it.

In case of the need for subsequent administration of oxytocin, a waiting period of at least 30 minutes is recommended following the removal of the vaginal insert (see Interactions).

Administration

MISODEL should only be administered by trained obstetric personnel in a hospital setting where continuous foetal and uterine contraction monitoring is available. The condition of the cervix should be assessed carefully before MISODEL is used. After MISODEL insertion, uterine activity and foetal condition must be carefully monitored by staff trained in cardiotocography interpretation. MISODEL should only be used in hospitals where facilities for emergency Caesarean delivery are readily available.

MISODEL is supplied in an individual aluminum foil sachet, and must be stored in the freezer. No thawing is required prior to use.

There is a “tear mark” on one side of the foil sachet. Open the foil sachet along the tear mark across the top of the sachet. Do not use scissors or other sharp objects which may cut the retrieval system.

Place MISODEL high in the posterior vaginal fornix (Figure a). To ensure that MISODEL remains *in situ*, it should be turned 90^{o} so that it lies transversely in the posterior fornix of the vagina (Figure b). Water-soluble lubricants may be used to aid insertion when necessary.

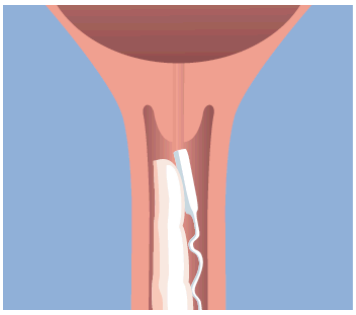


Figure a

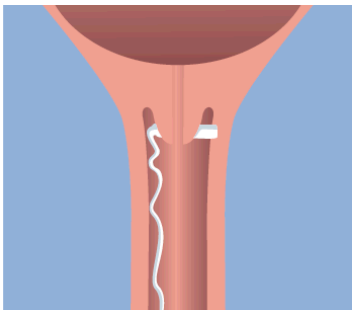


Figure b

Figure c

After MISODEL has been inserted, the withdrawal tape may be cut with scissors always ensuring there is sufficient tape outside the vagina to allow removal.

The patient is to remain in bed for 30 minutes after insertion, but may be ambulatory thereafter. Take care not to inadvertently remove MISODEL during toileting and vaginal examinations.

Removal
MISODEL is removed by gently pulling the tail of the retrieval system (Figure c).
The vaginal insert should NEVER be removed from the retrieval system.

MISODEL is a modified-release formulation that swells in the presence of moisture, causing drug release to occur. During insertion, MISODEL will swell to 2-3 times its original size and be pliable. After removal, ensure that the entire product (insert and retrieval system) has been removed from the vagina.

OVERDOSAGE

There is no experience with the use of more than one application of MISODEL. The controlled release formulation and ability to remove MISODEL thereby stopping misoprostol delivery limits the risk of overdose. Accidentally leaving MISODEL in place after onset of active labour may lead to symptoms of prostaglandin overdose (excessive uterine stimulation). If this occurs, remove MISODEL and manage in accordance with the local protocol.

PRESENTATION AND STORAGE CONDITIONS

MISODEL vaginal insert is rectangular in shape with rounded corners, is buff coloured, semi-transparent, non-biodegradable and measures approximately 30 mm in length, 10 mm in width and 0.8 mm in thickness. The polymer insert is contained within a retrieval system consisting of an inert woven polyester pouch and tail. Each vaginal insert is packed with a desiccant within an individual sealed laminated aluminium foil sachet.
MISODEL vaginal inserts are supplied in packs of 1s or 5s. Not all pack sizes may be marketed.

Storage conditions

Store below -18ºC. (Deep freeze).

MISODEL should be removed from the freezer and taken out of the laminated aluminium foil sachet just prior to insertion. However, controlled periods of time of up to one week at 2 to 8°C can be allowed within the shelf life of the product.

Once the MISODEL insert is removed from the freezer it may be stored for a period of up to one week in the refrigerator (2 to 8°C) prior to use. However, if the insert is not used during this period of storage in the refrigerator, it should be discarded, and must not be returned to the freezer for later use. If stored in the refrigerator, the date of removal from the freezer should be noted.

The whole product should be disposed as clinical waste following removal.

NAME AND ADDRESS OF SPONSOR

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Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

11 March 2014

DATE OF MOST RECENT AMENDMENT

14 January 2016