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MISODEL® 200 micrograms vaginal delivery system

FERRING PHARMACEUTICALS

PM-3274

QUALITATIVE AND QUANTITATIVE COMPOSITION

MISODEL contains 200 micrograms misoprostol.
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.
Excipients with known effect: 0.13 mg butylated hydroxyanisole per dose.

PHARMACEUTICAL FORM

Vaginal delivery system.
The polymer insert is contained within a retrieval system consisting of an inert woven polyester pouch and tail. The polymer insert is rectangular in shape with radiused corners, is buff coloured, semi-transparent, non-biodegradable and measures approximately 30mm in length, 10 mm in width and 0.8 mm in thickness. MISODEL swells in the presence of moisture.

CLINICAL PARTICULARS

Therapeutic indications

MISODEL is indicated for induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated.

Posology and method of administration

Posology

MISODEL 200 micrograms is a controlled release formulation that releases misoprostol at a rate of approximately 7 micrograms/hour over a period of 24 hours.The maximum recommended dose is one MISODEL vaginal delivery system (200 micrograms).

Remove MISODEL

- at the onset of active labour (progressive cervical dilatation to 4 cm with any frequency of contractions or rhythmic, firm, adequate quality uterine contractions causing progressive cervical change occurring at a frequency of 3 or more in 10 minutes and lasting 45 seconds or more)
- if uterine contractions are prolonged or excessive
- if there is evidence of fetal compromise
- if 24 hours have elapsed since insertion

If MISODEL falls out, do not replace it. In case of subsequent administration of oxytocin, a waiting period of at least 30 minutes is recommended following the removal of the vaginal delivery system.

Paediatric population

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

Method of administration

MISODEL should only be administered by trained obstetric personnel in a hospital setting where facilities for continuous fetal and uterine monitoring is available. The condition of the cervix should be assessed carefully before MISODEL is used. After insertion, uterine activity and fetal condition must be carefully monitored. MISODEL is supplied in an individual aluminium 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 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. 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.

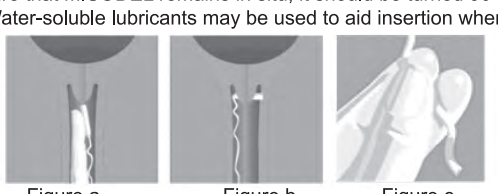

Figure a. Figure b. Figure c.

After 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.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 delivery system should NEVER be removed from the retrieval system.
MISODEL is a controlled 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.

Contraindications

MISODEL is contraindicated:
• When there is hypersensitivity to the active substance
• When labour has started
• When there is suspicion or evidence of fetal compromise prior to induction (e.g., failed non-stress or stress test, meconium staining or diagnosis or history of non-reassuring fetal status)
• When oxytocic drugs and/ or other labour induction agents are being given
• When there is suspicion or evidence of uterine scar resulting from previous uterine or cervical surgery, e.g. caesarean delivery
• 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 fetal malpresentation
• When there are signs or symptoms of chorioamnionitis, unless adequate prior treatment has been instituted
• Before week 36 of gestation.

Special warnings and precautions for use

MISODEL can cause excessive uterine stimulation if left in place after onset of active labour. 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 fetal compromise should be ruled out. 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 III 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 III 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. MISODEL has only been studied in singleton pregnancies with cephalic presentation. No studies in multiple pregnancies have been performed. MISODEL has not been studied in women with more than 3 previous vaginal deliveries after 24 weeks gestation. MISODEL should be used only 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.

Interaction with other medicinal products and other forms of interaction

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. 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.

Fertility, pregnancy and lactation

Fertility

From fertility and early embryonic development studies in rats, there is evidence of a possible adverse effect of misoprostol on implantation, however this is not relevant for the indicated clinical use of MISODEL.

Pregnancy

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

Breast-feeding

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 breast-fed newborns have been observed in the clinical development programme.

Effects on ability to drive and use machines: Not relevant.

Undesirable effects: Clinical Studies Experience

Summary of the safety profile

The adverse reaction profile below 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.

Adverse Reactions observed in Clinical Studies

Nervous system disorders: *Uncommon:* Hypoxic-ischaemic encephalopathy
Cardiac disorders: *Common:* Foetal heart rate disorder
Respiratory, thoracic and mediastinal disorders: *Uncommon:* Neonatal respiratory depression, Neonatal respiratory distress syndrome, Transient tachypnoea of the newborn
Gastrointestinal disorders: *Uncommon:* Nausea, Vomiting
Skin and subcutaneous tissue disorders: *Uncommon:* Rash
Pregnancy, puerperium and perinatal conditions: *Common:* Abnormal labour affecting foetus, Meconium in amniotic fluid, Uterine contractions abnormal
Uncommon: Antepartum haemorrhage, Foetal acidosis, Postpartum haemorrhage, Premature separation of placenta, Uterine hypertonus
Reproductive system and breast disorders: *Uncommon:* Pruritus genital
Investigations : *Uncommon:* Apgar score low, Blood pressure increased
Injury, poisoning and procedural complications: *Uncommon:* Uterine rupture

In the pivotal MISODEL study (Miso-Obs-303: The EXPEDITE Study), neonates were followed for the first month after delivery for hospital admission or emergency room visits. No adverse reactions were reported following hospital discharge.

Overdose

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 local protocol.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Mechanism of action

Misoprostol is a synthetic analogue of Prostaglandin E1 (PGE1), 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 the short treatment.

Pharmacokinetic properties

Misoprostol, an ester, is rapidly metabolised to its active metabolite misoprostol acid. Only misoprostol acid is detectable in plasma. The acid is further metabolised to inactive dinor and tetranor acid metabolites prior to excretion in the urine.
In non-pregnant women, the MISODEL vaginal delivery system 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 Cmax of 45.8 pg/mL with a median Tmax 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Cross-linked hydrogel polymer (compromised of macrogol 8000, 1,2,6- hexanetriol and dicyclohexyl-methane-4,4’-diisocyanate), Butylated Hydroxyanisole (Ph.Eur.), Polyester retrieval system (knitted polyester yarn)
Incompatibilities: Not applicable.
Shelf life: See outer carton.
Special precautions for storage: Store in a freezer (-10 to -25°C). No thawing is required prior to use.

Nature and contents of container

1 x 200 micrograms vaginal delivery system
5 x 200 micrograms vaginal delivery system
5 x 200 micrograms vaginal delivery system (multipack).
Each vaginal delivery system is contained within an individual foil sachet produced from an aluminium foil laminate strip containing a desiccant and packed in a carton.
Not all pack sizes may be marketed.

Special precautions for disposal and other handling

MISODEL should be removed from the freezer and taken out of the laminated aluminium foil sachet just prior to insertion.
Any unused medical product or waste material should be disposed of in accordance with local requirements. The whole product should be disposed following removal.

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PRESCRIPTION/PHARMACY STATUS: Prescription only

THIS IS A MEDICINE
- A MEDICINE IS A PRODUCT WHICH AFFECTS YOUR HEALTH, AND ITS CONSUMPTION CONTRARY TO INSTRUCTIONS IS DANGEROUS FOR YOU.
- STRICTLY FOLLOW THE DOCTOR'S PRESCRIPTION, THE METHOD OF USE AND THE INSTRUCTIONS OF THE PHARMACIST WHO SOLD THE MEDICINE.
- THE DOCTOR AND THE PHARMACIST ARE EXPERTS IN MEDICINE, ITS BENEFITS AND RISKS.
- DO NOT BY YOURSELF INTERRUPT THE PERIOD OR TREATMENT PRESCRIBED FOR YOU.
- DO NOT REPEAT THE SAME PRESCRIPTION WITHOUT CONSULTING YOUR DOCTOR.
- KEEP THE MEDICINE OUT OF REACH OF CHILDREN.

Council of Arab Health Ministers
Union of Arab Pharmacists