## 1. NAME OF THE MEDICINAL PRODUCT

Misofar 25 micrograms vaginal tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal tablet contains 25 micrograms of misoprostol.
Excipient(s) with known effect: each tablet contains 1.4 mg of hydrogenated castor oil.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Vaginal tablet.
Misofar 25 vaginal tablets are white, round with a cross-shaped mark on one side and 9 mm diameter.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Misofar 25 is an uterotonic agent, a synthetic analogue of prostaglandin $E_1$, which is indicated for cervical ripening and the induction of labour at term, especially in cases of unripe cervix, as long as there are no foetal or maternal contraindications.

### 4.2 Posology and method of administration

Posology

The dose must be adapted to the patient's response and must always be maintained at the lowest levels which produce a satisfactory uterine response.

The recommended dose is 25 micrograms of misoprostol every 4-6 hours, up to a maximum of 4 to 6 tablets.

*Pediatric population*
The safety and efficacy of Misofar 25 in women below 18 years old has not yet been established. No data is available.

Method of administration

The route of administration for Misofar 25 is vaginal.

The following recommendations of use must be followed:
- Wash your hands carefully.
- Take the vaginal tablet out from the blister.
- The patient will lay down on a gynaecological examination table and the doctor or midwife will administer the tablets by inserting them into the fornices of the vagina.

## 4.3 Contraindications

Administration of Misofar 25 is contraindicated in the following situations:

- Hypersensitivity to misoprostol, to prostaglandins or to any of the excipients listed in section 6.1.
- Patients in whom oxytocic drugs are generally contraindicated or if the prolonged uterine contractions are considered to be inappropriate.
- Patients having any of the following characteristics:
    - History of caesarean section or major uterine surgery.
    - Cephalopelvic disproportion.
    - Suspicion or clinical evidence of pre-existing foetal distress.
    - History of difficulty and/or traumatic childbirth.
    - Multiparous women with six or more previous term pregnancies.
    - Situations of foetus in transverse lie
    - In obstetric emergencies, when the benefit-risk ratio for the foetus and for the mother justifies surgical intervention.
    - Multiple pregnancy.
    - Unexplainable vaginal discharge and/or irregular uterine haemorrhage during the current pregnancy.
- Patients in whom vaginal delivery is contraindicated, such as cases of placenta praevia or active genital herpes.
- With simultaneous administration of oxytocin or other uterine contraction stimulants.
- Misofar 25 should not be administered in patients with risk factors of suffering amniotic fluid embolism, serious pre-eclampsia or eclampsia.

## 4.4 Special warnings and precautions for use

**In the absence of specific studies, use of Misofar 25 is not recommended in patients with:**

- **Renal impairment**
- **Hepatic impairment**
- **Malnutrition**

Misofar 25, like other potent uterotonic agents, should be used following strict observation of the recommended dose and dosage. It should only be used only in hospitals with access to intensive care and emergency surgery.

The following warnings should be taken into account:

- Cephalopelvic indexes must be carefully measured before using Misofar 25 (see section 4.3).
- Before and during use, uterine activity, foetal status and cervix characteristics (dilation and effacement) must be closely controlled, either by auscultation or electronic foetal monitoring, in order to detect possible evidence of undesirable responses such as hypertonus, sustained uterine contractility or foetal distress. In the event of patients developing uterine hypercontractility or hypertonus, or if the foetal heartbeat is not adequate, one must proceed so as not to cause risk to the mother or foetus. Like with other uterotonic agents, the risk of uterine rupture should be taken into account, especially if there is prior uterine scarring. The cervix must be assessed by performing normal gynaecological procedures such as vaginal-abdominal palpation.

An increased risk of postpartum disseminated intravascular coagulation has been described in patients whose labour has been induced by any physiological or pharmacological means.

In the event of bleeding, special attention should be paid to patients with haemostatic disorder accompanied with hypocoagulability or anaemia.

Misofar 25 shall be used with caution in patients with:

- Epilepsy or history of epilepsy.
- Renal and/or hepatic illness. In patients with moderate or serious renal and/or hepatic impairment, an increase in AUC, $C_{max}$ and $t_{1/2}$ has been observed, so in case of use in these patients a dosage adjustment will be necessary, though use of Misofar 25 is not initially recommended in these cases.
- Cardiovascular illness.
- Hypotension. Misoprostol can lead to arterial hypotension due to the peripheral vasodilator effect of prostaglandins.
- Chorioamniotic membranes rupture.
- Chorioamniotitis (infection of the placental membranes and of the amniotic fluid), hydatidiform mole and/or intrauterine foetal death.

Warnings about excipients
This medicine may cause skin reactions because it contains hydrogenated castor oil. Even though the amount contained in the preparation is probably insufficient to trigger this effect, this must be taken into account.

## 4.5 Interaction with other medicinal products and other forms of interaction

Misoprostol may increase the effect of oxytocin. The simultaneous administration of oxytocin along with other medicines which stimulate uterine contractions is contraindicated. In the event of there being a need to administer misoprostol and oxytocin consecutively, in the doctor’s opinion, the patient's uterine activity must be closely monitored.

Acenocumarol: A possible inhibition of the anticoagulant effect has been observed when used simultaneously with misoprostol.
Antacids: Antacids which contain magnesium may increase the frequency and intensity of diarrhoea associated with misoprostol.
NSAIDs: Possible increase in neurological toxicity (phenylbutazone, naproxen) and abdominal pain or diarrhoea (diclofenac, indomethacin) have been found in several studies.
Laxatives: Administration of laxatives together with misoprostol could lead to intense diarrhoea.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Misofar 25 is used for labour induction at a low misoprostol dosage for a short period of time at the very end of pregnancy. When used at that time of pregnancy, there is no risk of foetal malformations. Misofar 25 should not be used at any other time during pregnancy: a threefold increased risk of foetal malformations (including Moebius syndrome, amniotic band syndrome and central nervous system anomalies) has been reported in pregnancies exposed to misoprostol first trimester.

Lactation
Misoprostol is excreted in breast milk, but its concentration is insignificant 5 hours after it has been administered.

## 4.7 Effects on ability to drive and use machines

Misofar 25 has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

*Effects on mother:*
The adverse effects of Misofar 25 are, in general, a prolongation of its pharmacological action.
The most serious side effects that may arise are the following: drug hypersensitivity, uterine rupture and cardiac arrest.

The most common side effects are:
- Gastrointestinal disorders: nausea, vomiting, diarrhoea, and abdominal pain.

The following side effects has been described occasionally:
- Immune system disorders: hypersensitivity reactions.
- Psychiatric disorders: syncope, neurosis.
- Nervous system disorders: dizziness, confusion, drowsiness, headache, trembling, anxiety.
- Eye disorders: visual disorders and conjunctivitis.
- Cardiac disorders: hypertension, hypotension, cardiac arrhythmia.
- Vascular disorders: phlebitis, oedema, thromboembolism.
- Respiratory, thoracic and mediastinal disorders: coughing, dyspnoea, bronchitis, pneumonia, epistaxis.
- Skin and subcutaneous tissue disorders: skin rash, exanthematous eruption, dermatitis, alopecia.
- Musculoskeletal disorders: athralgia, myalgia, cramps and muscular stiffness, back pain.
- Renal and urinary disorders: There have been cases of polyuria and haematuria.
- Pregnancy, puerperium and perinatal conditions: abnormal uterine contractility (increased frequency, tone or duration) with or without foetal bradycardia, uterine rupture, premature membrane rupture, premature detachment of the placenta, amnionitis, pulmonary embolism due to amniotic fluid, vaginal haemorrhage.
- Reproductive system and breast disorders: dysmenorrhoea and vaginal haemorrhage appear rarely.
- General disorders and administration site conditions: transient hyperthermia, shivers.

*Effects on foetus:*
- Alteration in foetal heartbeat, foetal acidosis (pH of the umbilical arterial below 7.15, intrauterine foetal sepsis, foetal suffering, Meconium Aspiration Syndrome, neonatal suffering (lower Apgar index).

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 Spanish System of Pharmacovigilance for Medicinal Products for Human Use: www.notificaRAM.es.

## 4.9 Overdose

An overdose with Misofar 25 may manifest by means of hypertonic uterine contractions (with the risk of intrauterine foetal death), hyperthermia, tachypnea, hypotension, convulsions with shivers, agitation and emesis.

If uterine activity or side effects reach excessive intensity, the dosage will be reduced or treatment will be suspended.

In the event of massive overdose, the supportive treatment will be symptomatic. There is not specific antidote. Standard measures for disposal will be taken and symptomatic treatment will be instituted.

While it is unknown if misoprostol can be eliminated by haemodialysis, as its metabolism produces a compound similar to fatty acids, this is unlikely.

In the event of extreme uterine hypertonia or foetal suffering, appropriate obstetric procedures will be followed and it is advised that the labour is carried out in an expedited fashion.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: misoprostol, ATC code: G02AD06

Misoprostol is a synthetic analogue to PGE1. Its duration of therapeutic action is longer and more resistant to the immediate metabolism of the first step than natural synthesis prostaglandins. Misoprostol induces contraction of uterine muscles, acts as a blood vasodilator agent and as a slight bronchodilator over the bronchial smooth muscle. It also acts in the gastrointestinal tract to inhibit acid secretion by acting directly on gastric parietal cells, reducing pepsin production, stimulating duodenal secretion of bicarbonate and increasing gastric mucosa production.

The prostaglandins which play a more important role in gynaecology and obstetrics are those belonging to groups E and F. Unlike what occurs with oxytocin, whose myometrial receptors require induction phenomena which only occur in the advanced stage of gestation, prostaglandin receptors are present in all myometrial tissue both outside gestation and at any chronological point during gestation, which permits their use throughout the entire pregnancy and even outside it. Using changes in molecular structure which block its rapid metabolism, significant modifications in the duration of its action have been achieved, increasing its efficacy at low concentrations and reducing undesirable side effects.

Misoprostol, like other prostaglandins, produces cervical ripening, dilation and softening of the cervix, reducing the quantity of collagenous fibres and allowing a greater quantity of water to filter through them. Immediately afterwards, in the case of pregnancy, misoprostol also increases the frequency and intensity of the uterine smooth muscle contractions so that the fibres are all oriented in the direction of the tension being exerted upon them, thus facilitating expulsion of the uterine contents. These properties of misoprostol allow it to be used in cervical ripening prior to hysteroscopy and other gynaecological procedures which require entrance into the uterine cavity, in inducing labour, in the prevention and/or treatment of postpartum haemorrhage, or in pregnancy interruption, whether used alone or in combination with other abortive drugs.

Increasing renal flow, misoprostol improves the renal function of patients with kidney transplants, compensating for renal vasoconstriction produced by cyclosporine or other immunosuppressors.

### 5.2 Pharmacokinetic properties

<u>Absorption</u>
When administered vaginally, the bioavailability of misoprostol is three times greater than when administered orally. After vaginal administration, the plasma concentration of misoprostol gradually increases, reaching a maximum peak between 60 and 120 minutes later, and slowly declining to reach 61% of the maximum level 240 minutes after administration.

**Table 1:** Pharmacokinetic profile of misoprostol vaginal administration

| Variable | Vaginal (n = 10) |
|---|---|
| $\mathbf{C_{max}}$ (pg /mL) | 165 ± 86 |
| $\mathbf{T_{max}}$ (min) | 80 ± 27 |
| **AUC** $_{\mathbf{0\text{-}240\ min}}$ | 503.3 ± 296.7 |
| **AUC** $_{\mathbf{0\text{-}360\ min}}$ | 956.7 ± 541.7 |

Patients with hepatic diseases or moderate to serious renal insufficiency should adjust the dose of misoprostol as the $C_{max}$ and AUC values can reach almost double the concentration found in healthy patients.

Furthermore, some studies have found that vaginal pH can modify the pharmacokinetics of misoprostol when it is administered using this route, and this can influence its degree of absorption, though the results are not conclusive.

Distribution
Misoprostol acid, the principal active metabolite of misoprostol, strongly bonds to plasma proteins, with values around 80 - 90%. The bond between drug and plasma proteins is independent of the plasma concentration of misoprostol or its metabolites when it is administered at therapeutical doses. Misoprostol administration is thus not affected by the age of the patient or the concomitant administration of other drugs which also strongly bind to plasma proteins.

Biotransformation
Once absorbed, misoprostol undergoes intense and almost complete hepatic metabolism giving rise to metabolites such as its deacetylated derivative, which is responsible for its activity. This acid metabolite undergoes additional metabolism by fatty acid oxidation systems (β and ω oxidation), and then a later reduction of the ketone group generates compounds which are inactive.

Misoprostol does not induce or inhibit the cytochrome P450 oxidative enzyme system and thus does not produce interactions with medicines such as theophylline, warfarin, benzodiazepines or other drugs which use this metabolism pathway.

Elimination
Misoprostol is largely eliminated by metabolism and subsequent excretion through urine (73%), mainly as metabolites, and less than 1% remains unaltered. Low quantities have been found in faeces (15%), probably through biliary excretion.

## 5.3 Preclinical safety data

Misoprostol, at high doses, produces an increase in congenital anomalies in rats and rabbits, including anomalies in upper and lower extremities and in the central nervous system, with the first and second months of pregnancy being the period of maximum sensitivity. It has been observed that misoprostol has an embryotoxic effect in rats and rabbits, and any dose which produces a maintained increase of uterine tone may endanger the embryo or foetus.

In animals, the acute toxic effects of misoprostol are similar to those described for other prostaglandins: relaxation of smooth muscles, difficulty breathing and depression of the central nervous system.

According to tests in animals, clinical signs that may indicate an overdose of misoprostol are: diarrhoea and diminished motor activity in rodents; and emesis, convulsions, mydriasis and diarrhoea in dogs. There are no significant differences in $LD_{50}$ values with the different sexes and routes of administration; nor is there evidence of notable changes in the toxic clinical signs with respect to the sex, type of animal species or route of administration

The toxic dose of misoprostol in humans has not been determined.

During one long-term toxicology study of misoprostol in dogs, rats and mice, a reversible increase in the number of superficial gastric epithelial cells (hyperplasia) was observed.

Further evidence of long-term toxicity was also found in a study carried out on female mice that were administered from 100 to 1000 times the efficient human dose. These mice suffered hyperostosis (bone hypertrophy), principally in the sternum bone marrow. However, this was not the case in long term studies conducted in dogs and rats and there has been no sign of this in humans treated with misoprostol.

Several *in vitro* studies indicate that misoprostol is not mutagenic. Carcinogenicity tests have also been done on rats and mice, with doses of 24, 240 and 2400 μg/Kg/day for 104-106 weeks given to rats, and of 160, 1600 and 16000 μg/Kg/day for 91-94 weeks to mice. Results of these tests demonstrated that misoprostol does not cause or increase the frequency of the appearance of tumours and that the increase in number of gastric epithelial cells is the greatest morphological change found after long treatment with misoprostol, with this hyperplasia reversible as soon as administration of this drug was stopped.

Long term carcinogenicity studies carried out on mice who were given doses of up to 2400 μg/Kg/day for two years show that misoprostol is not carcinogenic.

More than 35 types of anomalies in children exposed to misoprostol during the first trimester of pregnancy have been described, and these can be categorised into anatomic groups. The defects most frequently described correspond to the lower extremities and appeared in four fifths of all cases (82.6%, n=57). More than half of cases (55.1%, n=38) presented anomalies in the central nervous system, while two fifths of cases (40.6%, n=28) and a quarter of cases (27.5%, n=19) presented anomalies in the upper extremities and in the skeletal system, respectively. Two fifths (40.6%, n=28) of cases presented other anomalies such as genital, eye or palate defects.

Published studies have identified effects on children whose mothers took misoprostol in a failed attempt to abort the pregnancy. The most common effects include *Moebius Syndrome* (congenital facial paralysis) and defects in the extremities. Even so, the absolute risk of acquiring this syndrome is relatively low among women exposed to misoprostol during the first trimester of pregnancy.

However, it must not be forgotten that the indication described in this summary of product characteristics is for cervical ripening and for inducing labour at term, so the teratogenic effects described above will have little relevance in this case.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Each tablet contains: hydroxypropyl methylcellulose, microcrystalline cellulose, sodium starch glycolate type A (potato) and hydrogenated castor oil.

### 6.2 Incompatibilities

None.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Aluminium/Aluminium blister.
Packaging with 8 vaginal tablets.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

Laboratorios BIAL, S.A.
C/ Alcalá 265, Edificio 2, Planta 2ª
28027 Madrid
Spain

## 8. MARKETING AUTHORISATION NUMBER(S)

69.682

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

March 2008

## 10. DATE OF REVISION OF THE TEXT

May 2019

Detailed information on this medicinal product is available on the website of Agencia Española de Medicamentos y Productos sanitarios: http://www.aemps.gob.es