1. NAME OF THE MEDICINAL PRODUCT

Misofar 200 micrograms vaginal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal tablet contains 200 micrograms of misoprostol.
Excipient(s) with known effect: each tablet contains 2 mg of hydrogenated castor oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal tablet.
The vaginal tablets of Misofar 200 are white, oblong capsular shaped, scored and 14x6 mm dimension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Misofar 200 is a synthetic analogue of prostaglandin E_1, which is indicated:
- for the expansion of non-gravid uterine cervix before a hysteroscopy or other gynaecological procedures requiring access to the uterine cavity.
- management of spontaneous or induced abortion incomplete without complications, in monotherapy or in association with mifepristone.

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 cause a satisfactory uterine response.

For the expansion of non-gravid uterine cervix before a hysteroscopy or other gynaecological procedures requiring access to the uterine cavity:
The recommended dose is 400 micrograms of misoprostol administrated from 2 to 8 hours before in cases without a medical history of previous caesarean or uterine scaring, and from 2 to 4 hours before in cases with a medical history of previous caesarean or uterine scaring.

For the medical management of incomplete abortion (spontaneous or induced)
The decision about the mode of management of incomplete abortion should be based on the individual's clinical condition and preference for treatment.
This medicinal product must be administered under the supervision of a healthcare professional capable of assessing the gestational age of the embryo and of diagnosing ectopic pregnancies (see section 4.3).

- For the medical management of incomplete abortion with an uterine size lower than 14 weeks: use of 600 µg misoprostol, in monotherapy or 1-2 days after administration of 200 mg of mifepristone (see section 4.4). Depending on clinical assessment and the different local recommendations or protocols 800 µg misoprostol may also be used. If necessary, additional doses can be administered after 24 hours.

- For the medical management of incomplete abortion with an uterine size of 14 weeks or higher: use of 400 µg misoprostol every 3 hours, in monotherapy or 1-2 days after administration of 200 mg of mifepristone (see section 4.4). Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process.
See section 4.4 on the administration of misoprostol in women with prior uterine incision.

Patients with renal or hepatic impairment:
It is not recommended the use of misoprostol in patients with severe renal or hepatic impairment due to lack of data (see section 4.4)

Pediatric population
The safety and efficacy of Misofar 200 in women below 18 years old has not yet been established. No data is available.

Method of administration

The route of administration for Misofar 200 is vaginal.

The following recommendations of use must be followed:
- Wash the hands carefully.
- Take out the vaginal tablet from the blister.
- The patient must lie on her back with the knees touching the chest.
- With the tip of the middle finger, place the vaginal tablet into the vagina as deep as possible without causing discomfort.

4.3 Contraindications

Administration of Misofar 200 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 the prolonged uterine contractions are considered to be inappropriate.
- - for the expansion of non-gravid uterine cervix before a hysteroscopy or other gynaecological procedures requiring access to the uterine cavity.
- Pregnancy or suspected pregnancy.
- - for management of spontaneous abortion incomplete without complications in association with mifepristone, or as standalone and for the management or induced abortion incomplete without complications, in association with mifepristone, or as standalone.
- Known or suspected ectopic pregnancy.

4.4 Special warnings and precautions for use

In the absence of specific studies, it's not recommended the use of Misofar 200 in patients with:

- **Renal failure**
- **Hepatic failure**
- **Malnutrition**

Misofar 200 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 failure, 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, although initially it is not recommended its use in these cases.

- Cardiovascular illness.
- Hypotension. Misoprostol could lead to arterial hypotension due to peripheral vasodilator effect of prostaglandins.
- History of caesarean section or major uterine surgery.
- In the event of a haemorrhage, special caution must be taken to patient with haemostatic disorder accompanied with hypocoagulability or anaemia.

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

The administration between mifepristone and misoprostol should be spaced 1-2 days, according to available information.

The risk of uterine rupture increases with gestational age. At gestational ages ≥ 14 weeks, caution should be exercised, and the maximum number of misoprostol doses in pregnant women with a previous uterine incision should be decided based on clinical judgment. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with advanced gestational age.

Patients should be warned about the occurrence of vaginal bleeding, sometimes prolonged and/or heavy, lasting 9 days or more after administration of misoprostol. Bleeding occurs in almost all cases and cannot be considered definitive proof of successful abortion.

When possible, Rh (Rhesus) group testing should be considered and administration of anti-D immunoglobulin when necessary to avoid Rh(D) isoimmunization in Rh(D) negative women.

Warnings about excipients
This medicine may cause allergic reactions on the application area because it contains hydrogenated castor oil..

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy
More than 35 types of anomalies in children exposed to misoprostol during the first quarter of pregnancy have been described. The most frequent defects were anomalies in lower extremities, central nervous system and genitals.

There have also been published effects on children whose mothers took misoprostol in a failed attempt to abort the pregnancy. Within the most common effects are *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 quarter of pregnancy.

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

4.8 Undesirable effects

The adverse effects of Misofar 200 are, in general, a prolongation of the 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:
- Infections and infestations: endometritis and pelvic inflammatory disease
- Gastrointestinal disorders: nausea, vomits, diarrhoea and abdominal pain.

The following side effects has been described occasionally:
- Infections and infestations: sepsis and septic shock
- Blood and lymphatic system disorders: anaemia
- 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: rarely dysmenorrhoea and vaginal haemorrhage appear.
- General disorders and administration site conditions: pyrexia, shivers and malaise.

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 Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: www.notificaRAM.es.

4.9 Overdose

An overdose with Misofar 200 may manifest by means of hypertonic uterine contractions, hyperthermia, tachypnea, hypotension or bradycardia, palpitations, convulsions with shivers, agitation, abdominal pain and emesis. Doses up to 1600 micrograms have been well tolerated.

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. It

is not known if misoprostol can be eliminated by haemodialysis, but taking into account that its metabolism produces a compound similar to fatty acids, this is unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: misoprostol, ATC code: G02AD06

Misoprostol is a synthetic analogue to PGE1. The duration of therapeutic action is higher and resist better the immediate metabolism of the first step than natural synthesis prostaglandins. It induces contraction of uterine muscle, acts as blood vasodilator agent and as slight bronchodilator over the bronchial smooth muscle. Also acts in the gastrointestinal tract inhibiting 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 most relevant role in gynecology 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 moment during gestation, and this circumstance permits their use throughout the entire pregnancy and even outside it. Using changes in molecular structure which permit blocking its rapid metabolism, significant modifications in the duration of its action have been achieved, which has increased its efficacy at low concentrations and reduced its undesirable adverse effects.

Misoprostol, as other prostaglandins, produces cervical ripening, dilation and softening of the cervix, reducing the quantity of collagenous fibers and allowing a greater quantity of water to filter through them. In the other hand, immediately afterwards, in case of pregnancy, misoprostol increases the frequency and intensity of the uterine smooth muscle contractions so that the fibers 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 a hysteroscopy and other gynecological procedures which require entrance into the uterine cavity, in inducing labor, in the prevention and/or treatment of postpartum hemorrhage or in pregnancy interruption, whether used alone or in combination with other abortive drugs.

On the other hand, increasing renal flow, misoprostol improve the renal function in patients with kidney transplants, compensating for renal vasoconstriction produced by cyclosporine or other immunosupressors.

A subgroup analysis on incomplete abortion from a systematic review and meta-analysis of randomised controlled trials assessing the effectiveness and safety of methods for miscarriage management, verified that three surgical methods (suction aspiration plus cervical preparation, dilatation and curettage, or suction aspiration), and two medical methods (mifepristone plus misoprostol or misoprostol alone) were found to be more effective than expectant management or placebo for providing a definitive treatment for an incomplete miscarriage. Expectant management or placebo has the lowest chance of successfully treating a miscarriage and has the highest chance of serious complications and the need for unplanned or emergency surgery.
The highest ranked method for managing a miscarriage for the outcome of complete miscarriage in the incomplete miscarriage subgroup was suction aspiration, followed by dilatation and curettage, misoprostol with mifepristone plus misoprostol ranked fourth and lastly expectant management or placebo. The evidence suggests that surgical treatment of a miscarriage does carry higher risks of pelvic infection compared to medical and expectant options.

5.2 Pharmacokinetic properties

Absorption
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, there are studies that allude to the fact that the vaginal pH can modify the pharmacokinetics of misoprostol when it is administered using this route, and this can influence its degree of absorption, although 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. Thus, misoprostol administration is 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 it does not produce interactions with medicines such as theophylline, warfarin, benzodiazepines and other drugs which use this metabolism pathway.

Elimination
Misoprostol is largely eliminated by metabolism and subsequent excretion through the urine (73%), mainly as metabolites and less than 1% remains unaltered. Low quantities have been found in feces (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, being the first and second month of pregnancy the period of most 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 fetus.

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 can indicate an overdose of misoprostol are: diarrhea and diminished motor activity in rodents; and emesis, convulsions, midriasis and diarrhea 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 neither there have been any 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, which were given doses of 24, 240 and 2400 µg/Kg/day for 104-106 weeks to rats, and doses 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 tumors and that the increase in number of gastric epithelial cells is the greatest morphological change found after long treatment with misoprostol, being 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 quarter of pregnancy have been described, and these can be categorized into anatomic groups. The defects most frequently described correspond to the lower extremities, and appeared in four fifths of all the cases (82.6%, n=57). More than half of the cases (55.1%, n=38) presented anomalies in the central nervous system, while two fifths of the cases (40.6%, n=28) and a quarter of the cases (27.5%, n=19) presented anomalies in the upper extremities and in the skeletal system, respectively. Two fifths (40.6%, n=28) of the cases presented other anomalies such as genital, eye or palate defects.

There have also been published effects on children whose mothers took misoprostol in a failed attempt to abort the pregnancy. Within the most common effects there are *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 quarter of pregnancy.

However, it must not be forgotten that the indications described in this summary of product characteristics are for cervical ripening prior to a hysteroscopy or any other gynaecological procedure requiring access to the uterine cavity and for the management of incomplete abortion (spontaneous or induced), so the teratogenic effects described above will have little relevance in these cases.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains: hydroxypropyl methylcellulose, microcrystalline cellulose, sodium starch glycolate type A (potatoe) 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 4 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.
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28027 Madrid
Spain

8. MARKETING AUTHORISATION NUMBER(S)

69.683

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

March 2008

10. DATE OF REVISION OF THE TEXT

September 2022

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