RSUMMARY OF PRODUCT CHARACTERISTICS

Product Name:	MISOFAR® 25 µg (Misoprostol)
Pharmaceutical form:	Vaginal tablet
Strength:	25 µg
Presentation	Case for 2 blisters of PA-AL-PVC/AL with 4 vaginal tablets each.
Marketing Authorisation holder:	BIAL-PORTELA & Ca S.A., Coronado, Portugal.
Manufacturing country:	INDUSTRIA QUÍMICA Y FARMACÉUTICA VIR, S.A., Madrid, España.
Number of registration:	M-18-068-G02
Date of approval:	August 2, 2018**.**
Composition:	
Each vaginal tablet contains:	
Misoprostol	0,025 mg
Hydrogenated recino oil	1,400 mg
Term of validity:	24 months
Storage conditions:	Store below 30°C.

Therapeutic indications

Misofar 25 is a uterotonic agent, synthetic analogue of prostaglandin E_1 that is indicated for cervical maturation and induction of labor at term, especially in cases of immature cervix, provided that there are no fetal or maternal contraindications.

Contraindications

Administration of Misofar 25 is contraindicated in the following situations:

Hypersensitivity to misoprostol, prostaglandins or any of the included excipients.

Patients in whom oxytocic drugs are generally contraindicated or in whom prolonged contractions of the uterus are considered inappropriate.

Patients who have any of the following characteristics: History of

cesarean section or major uterine surgery.

Cephalopelvic disproportion.

Suspected or clinical evidence of pre-existing fetal distress.

History of difficult labor and/or traumatic labor.

*translation not verified

Multiparous, with six or more pregnancies prior to term.

Transverse fetus situations.

In obstetric emergencies when the benefit-risk ratio for both the fetus and the mother advises surgical intervention.

Multiple pregnancy.

Unexplained vaginal discharge and/or irregular uterine bleeding during the current pregnancy.

Patients in whom vaginal delivery is not indicated, such as patients with placenta previa or active genital herpes.

Simultaneous administration of oxytocin or other stimulants of uterine contractions.

It should not be administered in patients with risk factors for amniotic fluid embolism, severe preeclampsia or eclampsia.

Precautions.

Misofar 25 should be administered with caution in patients with:

Epilepsy or a history of epilepsy.

Kidney and/or liver disease. In patients with moderate or severe renal and/or hepatic insufficiency, an increase in AUC, C_{max} and $t_{1/2}$ has been observed, so if used in these patients a dosage readjustment will be necessary, although initially its use is not recommended in these cases.

Cardiovascular disease.

Hypotension. Misoprostol may induce the onset of arterial hypotension by the peripheral vasodilator effect of prostaglandins.

Rupture of chorioamniotic membranes.

Chorioamnionitis (infection of placental membranes and amniotic fluid), hydatidiform mole and intrauterine fetal death.

Special warnings and precautions for use.

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

Renal and hepatic insufficiency and malnutrition.

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

The following warnings should be taken into account:

Cephalopelvic indices should be carefully measured before the use of Misofar 25.

Uterine activity, fetal status and characteristics of the cervix (dilation and erasure) should be thoroughly monitored before and during use, either by auscultation or by electronic fetal monitoring, to detect the possible occurrence of unwanted responses such as hypertonia, sustained uterine contractility or fetal distress. In the event that patients develop hypercontracttility or uterine hypertonia, or if the fetal heart rhythm is not adequate, it should be done in such a way that it does not pose a risk to either the mother or the fetus. As with other uterotonic agents,

the risk of rupture of the uterus should be considered, especially if there is a previous uterine scar. The cervix should be evaluated using the usual gynecological procedures, such as the vagino-abdominal touch

An increased risk of postpartum disseminated intravascular coagulation has been reported in women in whom labour has been induced by a physiological or pharmacological method.

In the event of bleeding, special attention should be paid to patients with hemostatic disorders accompanied by hypocoagulability or anemia.

Excipient Warnings

This medication may cause skin reactions because it contains hydrogenated castor oil. Although the amount present in the preparation is probably not sufficient to trigger this effect, it should be taken into account.

Undesirable effects.

Effects on the mother

The adverse effects of Misofar 25 are, in general, a prolongation of the pharmacological action.

The most serious adverse reactions that may occur are the following: hypersensitivity to the drug, uterine rupture and cardiac arrest.

The most common adverse reactions are:

Gastrointestinal disorders: nausea, vomiting, diarrhea and abdominal pain.

The following side effects have been occasionally described: Immune system

disorders: hypersensitivity reactions.

Psychiatric disorders: syncope, neurosis.

Nervous system disorders: dizziness, confusion, drowsiness, headache, tremors, anxiety.

Eye disorders: vision disorders and conjunctivitis. Cardiac disorders:

hypertension, hypotension, cardiac arrhythmia. Vascular disorders:

phlebitis, edema, thromboembolism.

Respiratory, thoracic and mediastinal disorders: cough, dyspnea, bronchitis, pneumonia, epistaxis.

Disorders of the skin and subcutaneous tissue: rash, rash rash, dermatitis, alopecia.

Musculoskeletal disorders: arthralgia, myalgia, muscle cramps and stiffness, back pain.

Renal and urinary disorders: Cases of polyuria and hematuria have been described.

Pregnancy, puerperium and perinatal diseases: abnormal uterine contractility (increased frequency, tone or duration) with or without fetal bradycardia, uterine rupture, premature rupture of membranes, placental abruption, amnionitis, pulmonary embolism due to amniotic fluid, vaginal bleeding.

Disorders of the reproductive system and breast: in rare cases dysmenorrhea and vaginal bleeding appear.

General disorders and alterations at the site of administration: transient hyperthermia, chills.

Effects on the fetus

Fetal heart rhythm disturbance, fetal acidosis (umbilical artery pH below 7.15, intrauterine fetal sepsis, fetal distress, meconium aspiration syndrome, neonatal distress (low Apgar assessment).

Reporting of suspected adverse reactions:

It is important to report suspected adverse reactions to the medicinal product after authorization. This allows for continuous monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are invited to report suspected adverse reactions through the Spanish Pharmacovigilance System for Medicinal Products for Human Use: https://www.notificaram.es.

Interaction with other drugs and other forms of interaction.

Misoprostol may potentiate the effect of oxytocin. Simultaneous administration of oxytocin and other drugs that stimulate uterine contractions is contraindicated. In the event that, in the opinion of the physician, misoprostol and oxytocin are deemed necessary consecutively, the patient's uterine activity should be carefully monitored.

Acenocoumarol: A possible inhibition of the anticoagulant effect has been observed, when used concomitantly with misoprostol.

Antacids: Antacids with magnesium may increase the frequency and intensity of diarrhea associated with misoprostol.

NSAIDs: Several studies have reported a possible potentiation of toxicity at the neurological level (phenylbutazone, naproxen) and abdominal pain or diarrhea (diclofenac, indomethacin).

Laxatives: Administration of laxatives along with misoprostol may result in severe diarrhea.

Dosage and mode of administration

Dosage

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

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

Pediatric population

The safety and efficacy of Misofar 25 in women under 18 years of age have not yet been established. No data available.

Method of administration

The route of administration of Misofar 25 is vaginal.

The following recommendations for use should be followed:

Carefully wash hands.

Remove the vaginal tablet from the blister.

The patient will be lying on a gynecological examination table, and the doctor or midwife will administer the tablets by inserting them into one of the vaginal fornix.

Use in Pregnancy and Lactation

Pregnancy

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

Effects have also been published on children of mothers who ingested misoprostol in a failed attempt to cause an abortion. Among the most common effects are *Moebius syndrome* (congenital facial paralysis) and limb defects. Even so, the absolute risk of suffering from this syndrome is relatively low among women exposed to misoprostol during the first trimester of pregnancy.

Nursing

Misoprostol is excreted in breast milk, but its concentration is negligible within 5 hours of administration.

Effects on the driving of vehicles/machinery.

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

Overdose

Overdosage with Misofar 25 may manifest with hypertonic uterine contractions (with risk of intrauterine fetal death), hyperthermia, tachypnea, hypotension, seizures with chills, agitation and emesis.

If uterine activity or side effects reach excessive intensity, the dose will be reduced or administration will be discontinued.

In the case of mass overdose, supportive treatment will be symptomatic. There is no specific antidote. The usual elimination measures will be carried out and symptomatic treatment will be established. It is unknown whether misoprostol can be eliminated by hemodialysis, but considering that its metabolism generates a compound similar to fatty acids, this does not seem very likely.

If extreme uterine hypertonicity occurs or if there is evidence of fetal distress, appropriate obstetric procedures will be followed and delivery is advised to be carried out quickly.

Pharmacodynamic properties

Pharmacotherapeutic group: Misoprostol, ATC code: G02AD06

Misoprostol is a synthetic analogue of prostaglandin E_1. The duration of therapeutic action is longer and better resists the immediate metabolism of the first-pass effect than naturally synthesized prostaglandins. It induces the contraction of the uterine musculature, acts as a dilating agent of blood vessels and as a slight bronchodilator on the bronchial smooth muscle fiber. It also acts on the gastrointestinal tract by inhibiting acid secretion by acting directly on gastric parietal cells, decreasing pepsin production, stimulating duodenal bicarbonate secretion, and increasing gastric mucus production.

The prostaglandins that have a more relevant role in gynecology and obstetrics are those belonging to groups E and F. Contrary to what happens with oxytocin, whose myometrial receptors require induction phenomena that only occur late in gestation, prostaglandin receptors are present throughout the myometrial tissue both outside gestation and at any chronological time of the same and this circumstance allows its use throughout the pregnancy and even outside it. Through changes in the molecular structure that allow to block its rapid metabolism, significant modifications are achieved in its duration of action, achieving a high efficiency with low concentrations and a decrease in undesirable adverse effects.

Misoprostol, like other prostaglandins, produces cervical ripening, dilation and softening of the cervix, decreasing the amount of collagen fibers and allowing a greater amount of water to be interspersed between them. On the other hand, and consecutively, in case of pregnancy misoprostol increases the frequency and intensity of contractions of uterine smooth muscle so that the fibers are oriented in the direction of the tension exerted on them, thus facilitating the expulsion of the uterine contents. These properties of misoprostol allow its use in cervical maturation prior to hysteroscopy or other gynecological procedures that require access to the uterine cavity, in the induction of labor, in the prevention or treatment of postpartum hemorrhage or in the termination of pregnancy, either alone or in combination with other abortifacient drugs.

On the other hand, by increasing renal flow, misoprostol improves renal function in kidney transplant patients, compensating for renal vasoconstriction produced by cyclosporine or other immunosuppressants.

Pharmacokinetic properties (Absorption, distribution, biotransformation, elimination):

Absorption

The bioavailability of misoprostol vaginally is three times greater than orally. After vaginal administration, the plasma concentration of misoprostol rises gradually, reaching the peak between 60 and 120 minutes, and slowly declines reaching 61% of the maximum level at 240 minutes after administration.

Table 1. Pharmacokinetic profile of vaginal misoprostol administration

Variable	Vaginal (n = 10)
$\mathbf{C_{max}}$ (pg/mL)	165 ± 86
$\mathbf{T_{max}}$ (min)	80 ± 27
$\mathbf{AUC_{0\text{-}240\ min}}$	503,3 ± 296,7
$\mathbf{AUC_{0\text{-}360\ min}}$	956,7 ± 541,7

Patients with liver disease or moderate to severe renal impairment should adjust the doses of misoprostol since the values of C_{max} and AUC can be almost double that in healthy patients.

*translation not verified

On the other hand, there are studies that allude to the fact that vaginal pH can modify the pharmacokinetics of misoprostol, when it is administered by this route, since it can influence the degree of absorption of it, although the results are not conclusive.

Distribution

Misoprostol acid, the main active metabolite of misoprostol, binds strongly to plasma proteins, with values around 80-90%. The binding of the drug to plasma proteins is independent of the plasma concentration of misoprostol or its metabolites, when administered at therapeutic doses. This means that its administration is not affected with the age of the patient or with the concomitant administration of other drugs that bind strongly to plasma proteins.

Biotransformation

Once absorbed, misoprostol undergoes an 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 an additional metabolism mediated by the oxidative systems of fatty acids (β and ω oxidation), and a subsequent reduction of the ketone group generates compounds lacking activity.

Misoprostol does not induce or inhibit the oxidative enzyme system of cytochrome P450, so it does not produce interactions with drugs such as theophylline, warfarin, benzodiazepines and other drugs that use this same metabolism pathway.

Elimination

Misoprostol is eliminated mainly by metabolism, and subsequent excretion in urine (73%), appearing in it in the form of metabolites fundamentally, with less than 1% in unchanged form. Small amounts have been found in feces (15%), probably by biliary elimination.

Instructions for use, handling and destruction of the unusable remnant of the product:

The disposal of the unused medicinal product and all materials that have come into contact with it shall be carried out in accordance with local regulations.

Date of approval/revision of the text: August 2, 2018.

*translation not verified