

1. NAME OF THE MEDICINAL PRODUCT

{Tradename} 400 microgram tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 400 microgram misoprostol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, flat tablets, with a diameter of 11 mm and thickness of 4.5 mm, with a break line on each side and double "M" engraved on one side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

For termination of pregnancy, the anti-progesterone mifepristone and the prostaglandin analogue misoprostol can only be prescribed and administered in accordance with the countries national laws and regulations.

4.1. Therapeutic indications

Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea (see section 4.2).

Cervix uteri preparation prior to surgical termination of pregnancy during the first trimester.

Misoprostol is indicated in adults.

4.2. Posology and method of administration

Posology

- Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea:

Misoprostol is taken as a single 400 microgram oral dose 36 to 48 hours after taking a single 600 mg oral dose of mifepristone. Information on the posology of mifepristone can be found in the product information of mifepristone.

Vomiting within 30 minutes after the intake could lead to a decrease in misoprostol efficacy: oral intake of a new misoprostol 400 microgram tablet is recommended in this case.

- Cervix uteri preparation prior to surgical termination of pregnancy during the first trimester:

Misoprostol is taken as a single 400 microgram oral dose 3 to 4 hours before surgical operation. Vomiting within 30 minutes after the intake could lead to a decrease in misoprostol efficacy: oral intake of a new misoprostol 400 microgram tablet is recommended in this case.

Paediatric population

Only limited data is available on the use of misoprostol in adolescents.

Method of administration

Misoprostol tablets are **for oral use only** and should not be administered by any other route of administration.

4.3. Contraindications

- ***In all instances***
 - Hypersensitivity to misoprostol or other prostaglandins, or to any of the excipients listed in section 6.1
 - Pregnancy not confirmed by ultrasound scan or biological tests
 - Suspected ectopic pregnancy
- ***For medical termination of pregnancy indication, in combination with mifepristone:***
 - Contraindication for mifepristone.
 - Pregnancy beyond 49 days of amenorrhoea,

When misoprostol is used in combination with mifepristone, please refer to the contraindications for this mifepristone as well.

4.4. Special warnings and precautions for use

- ***In all instances***

In the absence of specific studies, the misoprostol is not recommended for use in patients with:

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

Warnings

Because of its abortifacient properties, misoprostol should never be used in a woman with an ongoing pregnancy who wants to complete it.

The age of the pregnancy must be determined from the questioning and the clinical examination of the patient. Uterine ultrasound is always recommended.

Other

Due to presence of castor oil, there is a risk of sensitization.

Teratogenicity

Patients who decide to continue the pregnancy after treatment must be informed of the risk of teratogenicity. This risk is inherent to the mifepristone and misoprostol or misoprostol alone regimen

objective and is enhanced when regimens other than the one mentioned in section 4.2 Posology and method of administration is used. Exposure of the foetus to misoprostol or mifepristone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome and/or central nervous system anomalies (see section 4.6). A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialised centres.

Rhesus allo-immunisation

The termination of pregnancy requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.

Precautions for use

Cardiovascular risk

Rare but serious cardiovascular accidents (myocardial infarction and/or spasm of the coronary arteries and severe hypotension) have been reported following the intra vaginal and intra muscular administration of a high dose of prostaglandin analogue, including misoprostol. For this reason, women with risk factors for cardiovascular disease (e.g. age over 35 years with chronic smoking, hyperlipidemia, diabetes) or established cardiovascular disease should be treated with caution.

Contraception initiation after termination of pregnancy

During clinical trials, new pregnancies occurred between embryo expulsion and the resumption of menses. Therefore, when a termination of pregnancy conducted is medically confirmed, it is recommended to start contraception immediately.

- ***Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea***

Warnings

Misoprostol MUST BE USED by oral route only:
- at a dose not higher than 400 micrograms
- after a previous administration of 600 mg mifepristone
- Within the 36 – 48 hours interval after mifepristone intake

Use of off label regimen enhances ALL risks related to the method

This method requires an active involvement of the woman who should be informed of the method's requirements:

- the necessity to combine treatment with mifepristone to be administered 36 – 48 hours before administration of this product,
- the need for a follow-up visit within 14 to 21 days after the intake of mifepristone in order to check for complete expulsion,
- the possible failure of the method, leading to a pregnancy termination by a second termination of pregnancy procedure.

Because of possible acute effects of misoprostol, women should be fully counselled regarding the likely signs and symptoms they may experience and have direct access to the treatment centre by telephone or local access.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of mifepristone/misoprostol.

Risks related to the method:

The efficacy of the medical termination of pregnancy method decreases:

- When the labelled regimen is not strictly applied,
- With parity

Failures

The non-negligible risk of an on-going pregnancy occurs in 1% of the cases where the medical termination of pregnancy was within 49 days of amenorrhea and after oral administration. This risk makes the follow-up visit mandatory in order to check that the expulsion is completed. In rare case of non-complete expulsion, a surgical revision may be necessary.

Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 12 days or more after mifepristone intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The bleeding can occur very quickly after misoprostol intake, and sometimes later:

- in 60%, expulsion occurs within 4 hours following misoprostol intake
- in 40%, expulsion occurs within 24 to 72 hours following misoprostol intake.

Rarely the expulsion may occur before misoprostol administration (around 3% of cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go in the event of any problems emerging, particularly in the case of excessive vaginal bleeding. This is bleeding that lasts longer than 12 days and/or that is heavier than the normal menstrual bleeding.

A follow-up visit must take place within a period of 14 to 21 days after the intake of mifepristone to verify by the appropriate means (clinical examination, together with beta-hCG measurement or ultrasound scan) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an undiagnosed ectopic pregnancy, and appropriate treatment should be considered.

Since heavy bleeding requiring haemostatic curettage occurs in 0 to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder or the level of anaemia.

In the event of an ongoing pregnancy diagnosed after the follow-up visit, termination by a second termination of pregnancy procedure will be proposed to the woman.

Infection

Serious cases (including fatal cases) of toxic shock and septic shock following infections with atypical pathogens (*Clostridium sordellii* and *perfringens*, *Klebsiella pneumoniae*, *Escherichia coli*, group A *Streptococcus*), have been reported with the medical abortion, performed with unauthorised vaginal or buccal administration of misoprostol tablets.

Clinicians should be aware of this potentially fatal complication.

Precautions for use

Other

The precautions related to mifepristone should also be followed.

- *Cervical preparation before first trimester surgical termination of pregnancy.*

Warnings

***Misoprostol MUST BE USED by oral route only:
- at a dose not higher than 400 micrograms***

Use of off label regimen enhances ALL risks related to the method

- No data are available on cervical preparation with misoprostol prior to surgical termination of pregnancy beyond the first trimester,
- The patient should be informed about the specificities about the surgical method: local or a general anaesthesia and short hospitalization required,

Failure rate

Success rate of surgical abortion is above 97.7%, which means that the failure rate is about 2.3%. This risk makes the follow-up visit mandatory in order to check that the abortion is completed. In rare case of abortion failed, another procedure may be necessary.

Bleeding

The patient should be informed of possible occurrence of heavy vaginal bleeding after taking misoprostol. Consequently, Misoprostol should be preferably taken at the treatment centre before the surgical procedure.

Risk of abortion before the surgical procedure

There is a risk of abortion before the surgical procedure, even though this risk is low.

Complication of the surgical procedure

Rare complications include uterus damage.

Due to potential uterine rupture (very rare in the first trimester) and due to the lack of safety and efficacy studies in a scarred uterus, misoprostol must be used with caution in case of uterine fragility, in particular in case of significant multiparity or scarred uterus.

Misoprostol treatment must be systematically followed by surgical termination of pregnancy.

A follow-up visit must take place within a period of 14 to 21 days after the surgical termination of pregnancy. In case of fever, pain, bleeding that occur after the surgery this visit should be done immediately.

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

Misoprostol is predominantly metabolised via fatty acid oxidising systems and has shown no adverse effect on the hepatic microsomal mixed function oxidase (P450) enzyme system.

A decrease of the efficacy of misoprostol can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Limited evidence suggests that co-administration of NSAIDs on the day of misoprostol administration does not adversely influence the effects of mifepristone or misoprostol on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

Antacids may decrease the bioavailability of misoprostol.

Antacids containing magnesium may aggravate diarrhoea caused by misoprostol.

4.6. Fertility, pregnancy and lactation

Pregnancy

Failure of pregnancy termination (continuing pregnancy) has been associated with a 3-fold increased risk of birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, compared to control group (about 2%). In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking and deglutition and eye movements, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, olygodactyly, cleft palate inter alia), and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).

Women considering medical termination of pregnancy should be precisely counselled on the risks to their foetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.

Consequently:

- Women should be informed, that due to the risk of failure of the method of pregnancy termination and to the risk for the foetus, the follow-up visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the follow-up visit (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by a second termination of pregnancy procedure.
- Should the patient wish to continue with her pregnancy, a careful ultrasound scan monitoring of the pregnancy, with a special attention to the limbs and head, must be established in a specialised centre.

Breast feeding

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Misoprostol may also be excreted in breast milk and consequently, women should avoid breastfeeding while taking mifepristone and misoprostol or misoprostol alone.

Fertility

Misoprostol does not affect fertility. It is possible that the woman becomes pregnant again as soon as the termination of pregnancy is completed. Therefore it is important to inform the patient to start contraception immediately after the termination of the pregnancy is confirmed.

4.7. Effects on ability to drive and use machines

No data showing an effect on the ability to drive are known. Dizziness could occur as a side effect. When driving or using machines one should take this possible side effect into account.

4.8. Undesirable effects

The side effects of misoprostol are usually an extension of the pharmacological action and of the drug bioavailability. The most common adverse reactions are gastrointestinal disorders e.g. nausea, vomiting, diarrhoea and abdominal pain.

The frequencies of occurrence of side effects are classified as follows:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1.000$ to $< 1/100$)

Rare ($\geq 1/10.000$ to $< 1/1.000$)

Very rare ($< 1/10.000$)

Not known (cannot be estimated from the available data)

Infections and infestations

Common:

- Infection following abortion. Suspected or confirmed infections (endometritis, pelvic inflammatory disease) have been reported in less than 5% of women.

Very rare:

- Very rare cases of serious or fatal toxic and septic shocks (caused by *Clostridium sordellii* or *perfringens*, *Klebsiella pneumoniae*, *Escherichia coli*, group A *Streptococcus*), which can be with or without fever or other obvious symptoms of infection, have been reported with the use of unauthorised vaginal or buccal administration of misoprostol tablets. Clinicians should be aware of this potentially fatal complication (see section 4.4. – Special warnings and special precautions for use).

Immune system disorders

Not known:

- Anaphylaxis, hypersensitivity.

Nervous system disorders

Rare:

- Headache.

Vascular disorders

Rare but serious cardiovascular accidents (myocardial infarction and/or spasm of the coronary arteries and severe hypotension) have been reported mainly with the use of non-authorized vaginal administration of misoprostol tablets.

Gastrointestinal disorders

Very common:

- Nausea, vomiting, diarrhoea (these gastro-intestinal effects related to prostaglandin use are frequently reported).

Common:

- Cramping, light or moderate.

Skin and subcutaneous tissue disorders

Uncommon

- Hypersensitivity: Skin rashes uncommon (0.2%).

Rare:

- Single cases of urticaria, erythroderma, erythema nodosum, toxic epidermal necrolysis have also been reported.

Very rare:

- Angioedema

Musculoskeletal and connective tissue disorders

Not known

- Back pain.

Reproductive system and breast disorders

Very common:

- Very common uterine contractions or cramping (10 to 45%) in the hours following misoprostol intake.
- Uterine bleeding

Common:

- Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.

Congenital, familial, and genetic disorders

Common:

- foetal malformations

Rare:

- foetal death.

General disorders and administration site conditions

Rare:

- Malaise, vagal symptoms (hot flushes, dizziness, chills), fever.

Injury, poisoning and procedural complication

Rare:

- Uterine rupture: uterine rupture has been uncommonly reported after prostaglandin intake for induction of termination of second trimester pregnancy or labour induction for foetal death in utero in the third trimester. Uterine ruptures occurred particularly in multiparous women or in women with a caesarean section scar.

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 national reporting system listed in Appendix V](#).

4.9. Overdose

In the event of overdosage, symptomatic treatment and appropriate medical care should be done. Gastrointestinal haemorrhage, renal failure, acute rhabdomyolysis, uterine haemorrhage and death have been reported after a massive dose of 12 mg misoprostol.

Symptoms related to an overdose of misoprostol: sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, haemorrhage, spasm of coronary arteries, hypotension, and bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: Other gynaecological drugs, oxytocics - prostaglandins

ATC code: G02AD06

- *In all instances*

At the recommended dosage, misoprostol (a synthetic analogue of prostaglandin E₁) induces contractions of smooth muscle fibres of the myometrium and a relaxation of the cervix uteri. The uterotonic properties of misoprostol should facilitate the opening of the cervix uteri.

At the recommended dosage, misoprostol should not involve cardiac, hepatic or renal undesirable effects.

- *Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea*

Misoprostol is used in combination with mifepristone for the termination of pregnancies of ≤ 49 days of amenorrhea.

In the event of an early termination of pregnancy, the combination of mifepristone-misoprostol leads to an increase in the success rate to about 95% of the cases and accelerates the expulsion of the conceptus. The success rate is around 95 % when 600 mg mifepristone is combined with misoprostol 400 microgram orally up to 49 days of amenorrhea.

The uterotonic properties of misoprostol should facilitate the opening of the cervix uteri and the expulsion of intra-uterine remains.

5.2. Pharmacokinetic properties

Absorption

Misoprostol is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite (misoprostol acid) occurring after about 30 minutes. The plasma elimination half-life of misoprostol acid is 20-40 minutes.

Distribution

The free acid of misoprostol is less than 90 % bound to plasma proteins. Misoprostol is metabolised by fatty acids-oxidising systems, present in several organs of the human body.

Elimination

After oral administration of ³H-misoprostol approximately 73 % of the radioactivity is excreted in urine and approximately 15 % in the faeces. Approximately 56 % of total radioactivity is eliminated within 8 hours via urine.

Administration of misoprostol with food does not change the bioavailability of misoprostol acid, but reduces the maximum plasma concentration due to a slower absorption rate.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

At high repeated doses in rats and rabbits, misoprostol was foeto- and embryotoxic. No teratogenic potential was observed.

In single- and repeat-dose studies in dogs, rats and mice at multiples of the human dose, toxicological findings were consistent with the known pharmacological effects of the E-type prostaglandins, the main symptoms being diarrhoea, vomiting, mydriasis, tremors and hyperpyrexia.

Intra-uterine but not the intragastric delivery of misoprostol to rats significantly worsened mortality from *Clostridium sordellii* uterine infection, and impaired bacterial clearance in vivo.

Misoprostol has been shown to alter calcium homeostasis in neuro-2a cells and contribute to abnormal cell function in vitro. Imbalances in calcium homeostasis can potentially affect early neuronal development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose,
Hypromellose,
Sodium starch glycolate (type A),
Hydrogenated castor oil.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

PVC-PCTFE/Alu blister: 1 year.
OPA-Alu-PVC/Alu blister: 2 years.

6.4. Special precautions for storage

Store below 25°C.
Any tablet stored outside the blister or not used immediately has to be discarded.

6.5. Nature and contents of container

1, 4, 16 or 40 tablet per carton box
Tablets are packed in perforated unit-dose PVC-PCTFE/Alu or OPA-Alu-PVC/Alu blister.
Not all pack sizes may be marketed

6.6. Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements

{Tradename} 400 microgram tablets

7. MARKETING AUTHORIZATION HOLDER

EXELGYN
216 boulevard Saint-Germain
75007 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

<Date of latest renewal: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>