PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]MIFEGYMISO

Mifepristone tablet
200 mg
Progesterone receptor modulator

and

Misoprostol tablets
200 mcg
Prostaglandin

Sponsor:
Linepharma International Limited
338 Regent's Place, Euston Road,
London, NW1 3BT
United Kingdom

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Mifegymiso
mifepristone tablet/misoprostol tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Mifegymiso (mifepristone tablet/misoprostol tablets) is a composite pack containing mifepristone 200 mg tablet and misoprostol 200 mcg tablets.

Product Name	Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
mifepristone	Oral	Tablet/200 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*
misoprostol	Buccal	Tablet/200 mcg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Mifegymiso (mifepristone tablet/misoprostol tablets) is indicated for medical termination of a developing intra-uterine pregnancy with a gestational age up to 49 days as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle.

Geriatrics:
Mifegymiso is not indicated in post-menopausal women.

Pediatrics (less than 18 years of age):
There are insufficient data in patients less than 15 years old to establish efficacy and safety. Mifegymiso is not indicated in the prepubertal population.

Compared to adults, patients less than 18 years of age reported nausea and pain more frequently (see WARNINGS AND PRECAUTIONS, *Special Populations, Pediatrics* and CLINICAL TRIALS).

Limitations of use:

Mifegymiso is not intended for routine use as a contraceptive.

Prior to prescribing Mifegymiso, physicians must:

- Ensure that patients have access to emergency medical care in the 14 days following administration of mifepristone;
- Schedule follow-up 7 to 14 days after patients take mifepristone to confirm complete pregnancy termination;
- Exclude ectopic pregnancy and confirm gestational age by ultrasound.
- Counsel each patient on the risks and benefits of Mifegymiso, including bleeding, infection and incomplete abortion;
- Obtain the patient's written informed consent to take the drug;
- Complete the mandatory Mifegymiso education and registration programs.

CONTRAINDICATIONS

Mifegymiso should not be prescribed to patients who:

- have an ectopic pregnancy;
- have an intrauterine device (IUD) in place;
- have unconfirmed gestational age;
- have chronic adrenal failure;
- are on concurrent long term systemic corticosteroid therapy;
- have haemorrhagic disorders or using concurrent anticoagulation therapy;
- have inherited porphyria;
- have uncontrolled asthma;
- have known hypersensitivity to mifepristone, misoprostol, other prostaglandins, or any of the excipients used in Mifegymiso. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

It is important that all patients be followed by a physician 7 to 14 days after taking mifepristone to confirm safety and complete pregnancy termination (see WARNINGS AND PRECAUTIONS, *Genitourinary*, *Failures* and *Monitoring and Laboratory Tests*).

Risk of infection and sepsis: Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of Mifegymiso. Some patients presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out sepsis (from e.g. Clostridium sordellii) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol (see WARNINGS AND PRECAUTIONS, *Genitourinary*).

Risk of bleeding: Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. These patients must seek immediate medical attention (see WARNINGS AND PRECAUTIONS, *Genitourinary*).

Embryotoxicity: Patients should be counselled that once the treatment is started, there are risks of embryotoxicity if the pregnancy is not terminated. Both mifepristone and misoprostol are embryotoxic and have been associated with fetal abnormalities (see TOXICOLOGY, *Reproductive and developmental studies*).

Return to fertility: Patients should be advised of their immediate return to fertility after Mifegymiso administration. To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive methods should therefore commence as early as possible (see WARNINGS AND PRECAUTIONS, *Special Populations, Pregnant Woman*).

General

A patient's ability to comply with the requirements of the regimen, especially the need for a follow-up visit, should be considered prior to administering Mifegymiso.

Patients should be advised to take their Patient Information Card with them if they visit an emergency room or another health care provider who did not prescribe Mifegymiso, so that provider will be aware that the patient is undergoing a medical abortion.

Rhesus alloimmunisation

The use of Mifegymiso requires measures to prevent rhesus alloimmunisation.

Genitourinary

Ultrasound must be performed before prescribing Mifegymiso. Physicians should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy, since some of the symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy.

Treatment failures

Failures in clinical studies occurred in 2.0 to 4.8% of cases prior to 49 days of gestation (see CLINICAL TRIALS). Reasons for failure requiring a surgical termination of pregnancy included persistent non-viable pregnancies, continuing pregnancies and persistent heavy vaginal bleeding. Follow-up is mandatory to ensure that the expulsion is completed.

In the event of an ongoing pregnancy, pregnancy termination should be completed by another method (see WARNINGS AND PRECAUTIONS, *Special Populations, Pregnant Woman*). Animal studies have shown that, if a pregnancy continues after exposure to mifepristone or misoprostol, fetal abnormalities may occur (see TOXICOLOGY, *Reproductive and developmental studies*).

Bleeding

Bleeding occurs in almost all cases and is not proof of complete expulsion (see CLINICAL TRIALS). Prolonged heavy vaginal bleeding may occur and can be a sign of incomplete expulsion. Bleeding can lead to a significant decrease in hemoglobin levels and may necessitate a blood transfusion.

Persistent bleeding should be monitored closely.

The patient should have access to emergency medical care until complete termination of pregnancy is confirmed at a follow-up visit.

Infections

Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone and misoprostol. A sustained fever of 38^{o}C or higher, severe abdominal pain or pelvic tenderness in the days after a medical abortion may be an indication of infection.

Sepsis (from e.g. *Clostridium sordellii* or other species e.g. *Streptococcus*) should be highly suspected if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. However, the symptoms of *Clostridium sordellii* infection are sometimes not the usual symptoms of sepsis. Very rarely, deaths have been reported. Therefore, the possibility of sepsis should be considered in all women who present with nausea, vomiting, diarrhoea and weakness with or without abdominal pain or fever. Strong consideration should be given to obtaining a complete blood count in these patients. Significant leukocytosis with a marked left shift and hemoconcentration

may be indicative of sepsis. Doctors should consider immediately initiating treatment with antibiotics that include coverage of anaerobic bacteria such as *Clostridium sordellii*.

Hematologic

Heavy bleeding requiring curettage occurred in some patients in clinical trials. Patients with anemia should be treated with caution. Patients with severe anemia were excluded from clinical trials and administration of Mifegymiso in these patients is not recommended.

Sexual Function/Reproduction

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid the potential exposure of a subsequent pregnancy to mifepristone and misoprostol, conception should be avoided during the next menstrual cycle. Reliable contraceptive precautions should commence as early as possible after Mifegymiso administration (see WARNINGS AND PRECAUTIONS, *Special Populations, Pregnant Women*).

Cardiovascular

Rare serious cardiovascular accidents have been reported following administration of prostaglandins including misoprostol. Mifegymiso has not been studied, and is therefore not recommended, in women with cardiovascular disease, hypertension, diabetes or who are over the age of 35 and are heavy smokers.

Women with risk factors for cardiovascular disease should be treated with caution.

Endocrine and Metabolism

Patients with suspected acute adrenal failure were excluded from trials and therefore should be treated with caution. If treatment with Mifegymiso is required, therapy should be adjusted. The safety and efficacy have not been studied in women suffering from malnutrition. Treatment with Mifegymiso is therefore not recommended.

Hepatic/Billiary/Pancreatic

The safety and efficacy have not been studied in women suffering from hepatic failure. Treatment with Mifegymiso is therefore not recommended.

Immune

Cases of skin rash following misoprostol administration were reported by patients in clinical trials. Angioedema of the face, lips, tongue, and/or larynx, including cases of anaphylaxis have been reported in post-market surveillance with the use of Mifegymiso, including angioedema occurring within an hour of misoprostol intake. Angioedema associated with upper airway swelling may be life threatening. If the tongue, hypopharynx, or larynx has been involved, appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Neurologic

Seizures have been reported with prostaglandins and prostaglandin analogues, and therefore this possibility should be considered when treating patients with a history of a seizure disorder.

Renal

The safety and efficacy have not been studied in women suffering from renal failure. Treatment with Mifegymiso is therefore not recommended.

Respiratory

Due to the antiglucocorticoid activity of mifepristone, the efficacy of corticosteroid therapy, including inhaled corticosteroids, may be decreased temporarily following intake of mifepristone. Therapy should be adjusted.

Bronchospasm may occur with some prostaglandins and prostaglandin analogues. Caution should be exercised in patients with a history of asthma (see CONTRAINDICATIONS).

Special Populations

Pregnant Women:

Mifepristone

Reproductive studies conducted in rabbits and monkeys have shown that if a pregnancy continues after exposure to mifepristone, abnormalities in fetal skull, brain and developmental markers may occur (see TOXICOLOGY, *Reproductive and developmental studies*).

A review of births from 105 pregnancies exposed during first trimester of pregnancy to mifepristone alone (46 cases) or to both mifepristone and misoprostol (59 cases) has been published[1]. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI: 1.2 – 10.4%), with two cases among 38 patients exposed to mifepristone alone and two cases among 57 patients exposed to both mifepristone and misoprostol.

Misoprostol

Use of misoprostol has been associated with birth defects. When used alone to induce an abortion, the following effects of misoprostol have been reported: malformations of limbs, abnormalities of fetal movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements).

Misoprostol was shown to be embryotoxic in rabbits, rats and mice, when exposure occurred during embryogenesis. There was also an increase in skeletal abnormalities in rabbits and cleft palate in mice (see TOXICOLOGY, *Reproductive and developmental studies*).

Mifegymiso

Due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the fetus, follow-up is mandatory (see WARNINGS AND PRECAUTIONS, *Boxed Serious Warnings and Precautions*).

Should a failure of Mifegymiso be diagnosed at follow-up (viable ongoing pregnancy), it is recommended that pregnancy termination should be completed by another method.

Should the patient wish to continue with the pregnancy, she should be appropriately counselled as to the risk of birth defects and appropriate ultra-sonographic monitoring of the pregnancy should be carried out.

Nursing Women:

Mifegymiso use should be avoided during breast-feeding.

Mifepristone is lipophilic and may be excreted in the mother's milk. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. This could cause undesirable effects such as diarrhea in breastfeeding infants.

Pediatrics (less than 18 years of age):

There are insufficient data in patients less than 15 years old to establish efficacy and safety. Mifegymiso is not indicated in the prepubertal population.

Patients 15 to 17 years of age had similar efficacy to that seen in the adult population. More pain than expected was reported more frequently in this population, as well as diarrhea and vomiting, compared with adults (see CLINICAL TRIALS). Careful counselling should be provided to adjust patients' expectations from the procedure and identification of safety issues requiring immediate medical attention.

Geriatrics:

Mifegymiso is not indicated in post-menopausal women.

Renal and hepatic impairment:

No studies were conducted in patients with renal or hepatic impairment.

Monitoring and Laboratory Tests

Follow-up must take place within a period of 7 to 14 days after administration of Mifegymiso to verify that expulsion has been completed (clinical examination, ultrasound scan or beta-hCG measurement). Persistent bleeding should be monitored closely for a decrease in hemoglobin concentration, hematocrit and red blood cell count.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequent undesirable effects which were observed during treatment with Mifegymiso were:

- Reproductive system disorders: vaginal bleeding, sometimes heavy and prolonged uterine cramping (see WARNINGS AND PRECAUTIONS, *Genitourinary*).
- Gastrointestinal disorders: nausea, vomiting, diarrhea and abdominal pain.
- General disorders: headache, dizziness, chills and fever.

Bleeding was occasionally observed after mifepristone alone. Misoprostol administration resulted in vaginal bleeding, abdominal pain and cramping. In some patients, persistent or heavy vaginal bleeding required treatment with intravenous fluids or blood transfusion. On average, bleeding lasted for 11 days and was heavier than a normal period for 2 days.

Infectious complications, including sometimes fatal sepsis, have been observed. Patients typically presented with abdominal pain or discomfort, fever or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol. *Clostridium sordellii* infection was observed in some women without abdominal pain or fever, that progressed rapidly to multi-organ failure and death.

The adverse events reported with Mifegymiso, classified according to frequency and system organ class, are summarized as shown in Table 1.

Table 1: Adverse Events for the Use of Mifepristone and Misoprostol

MedDRA	Adverse events (frequency)		
System Organ Class	**Very common (≥ 1/10)**	**Common (> 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**
Gastro-intestinal disorders	Nausea; Vomiting; Diarrhea; Gastric discomfort; Abdominal pain	Cramping, light or moderate	
Cardiac disorders			Arrhythmia
Nervous system disorders	Headache		
Reproductive system & breast disorders	Vaginal bleeding; Spotting; Uterine contractions or cramping	Prolonged post-abortion bleeding; Severe hemorrhage; Endometritis; Breast tenderness; Heavy bleeding; Heavy bleeding requiring surgical termination of pregnancy	Hemorrhagic shock; Salpingitis; Heavy bleeding requiring IV fluids or blood transfusion
General disorders and administration site conditions	Fatigue; Chills / fever; Dizziness	Fainting	
Infections and infestations			Infection
Vascular disorders			Hot flush; Hypotension
Respiratory, thoracic and mediastinal disorders			Bronchospasm
Skin and subcutaneous tissue disorders			Skin rash / pruritus

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Mifegymiso was studied in three open-label multi-center prospective studies. In these studies, a total of 898 women were included in the safety analysis. The mean age of women who received mifepristone and misoprostol was 26.5, 26.8 and 25.5 years for Studies 1, 2 and 3, respectively.

Table 2: Treatment-Emergent Adverse Events Occurring in Clinical Trials, %

Adverse Events	**Study 1**	**Study 2**	**Study 3**
	N = 143	**N = 204**	**N = 551**
Nausea	69.2	65.6	30.7
Vomiting	30.1	34.1	22.3
Diarrhea	36.4	31.8	58.6
Pain	91.6	-	-
Fever	38.5	21.3	44.3
Chills	-	36.5	
Headache	42	32.7	12.3
Dizziness	45.5	37	13.1
Weakness	56.6	46.4	19.2

Study results in women less than 18 years of age

Of the 551 women enrolled in Study 3, 35 were less than 18 years of age. The reported frequent adverse events are detailed below:

Table 3: Adverse events by age

Adverse Events	< 18 years	≥ 18 years
	N = 35	N = 516
Nausea	34.3%	30.4%
Vomiting	42.9%	20.9%
Diarrhea	65.7%	58.1%
Fever/chills	40%	44.6%
Headache	5.7%	12.8%
Dizziness	17.1%	12.8%
Weakness	17.1%	19.4%

DRUG INTERACTIONS

Overview

No interaction studies have been performed with mifepristone and misoprostol.

Drug-Drug Interactions

Mifepristone

In vitro studies showed mifepristone to be metabolized by CYP3A4 and that co-administration of other CYP3A4 substrates inhibited metabolite formation. CYP3A4 inhibitors, such as ketoconazole, itraconazole and erythromycin may inhibit mifepristone metabolism, whereas CYP3A4 inducers, such as rifampicin, dexamethasone, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine), may increase its metabolism.

In vitro studies also showed mifepristone to be a competitive inhibitor of CYP3A4 and, to a lesser extent, of CYPs 1A, 2B, 2D6, and 2E1.

Due to the irreversible nature of the CYP binding and the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

Due to the antiglucocorticoid activity of mifepristone, the efficacy of corticosteroid therapy, including inhaled corticosteroids, may be temporarily decreased following intake of mifepristone. Therapy should be adjusted.

Misoprostol

Limited studies investigating the metabolism of misoprostol were conducted in the rat.
Misoprostol was not found to affect hepatic drug metabolism.

No drug interactions have been attributed to misoprostol in extensive clinical trials.

Drug-Food Interactions

Grapefruit juice may inhibit mifepristone's metabolism, increasing its serum levels.

Drug-Herb Interactions

The concomitant use of St. John's wort may increase mifepristone metabolism, lowering its serum levels.

Drug-Laboratory Test Interactions

There are no known effects of mifepristone or misoprostol on laboratory tests.

Drug-Lifestyle Interactions

Mifepristone and misoprostol may cause dizziness, which could have an effect on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Before starting Mifegymiso, patients must be informed of the following:

- Mifepristone and misoprostol must be taken in sequence according to instructions.
- Follow-up within 7 to 14 days after intake of mifepristone to confirm pregnancy termination and complete abortion is required.
- Return to fertility is expected immediately after Mifegymiso administration and reliable contraceptive methods should be started as early as possible.
- Failure of Mifegymiso may require surgical termination of pregnancy (see CLINICAL TRIALS).
- Signs and symptoms they may experience.
- How to access emergency medical care by telephone or local access.

Each patient must be provided with a printed copy of the Mifegymiso Patient Medication Information document and a Patient Information Card.

Recommended Dose and Dosage Adjustment

Mifepristone:
200 mg of mifepristone (1 tablet) should be taken orally, followed 24 to 48 hours (1 to 2 days) later by the administration of misoprostol.

Mifepristone should be administered under the supervision of the prescriber. In the clinical trials supporting Mifegymiso efficacy and safety, mifepristone was administered under the supervision of a physician in a clinical setting.

Misoprostol:
800 mcg of misoprostol (4 tablets, each tablet containing 200 mcg) should be taken in a single intake by buccal route (kept between the cheek and the gum for 30 minutes before any remaining fragments are swallowed with water).

There are no data available on the effect of food intake on the absorption of mifepristone or misoprostol.

Missed Dose:

Patients should be advised to contact their doctor immediately if they forget to take the Misoprostol tablets and it is more than 48 hours after they have taken the Mifepristone tablet.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Mifepristone

No cases of overdose have been reported.

In the event of massive ingestion of mifepristone signs of adrenal failure may occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

Misoprostol

Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort reported.

Possible symptoms of an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhea, fever, palpitations, hypotension or bradycardia. Hypertension and tachycardia have also been reported.

There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of misoprostol if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

When mifepristone blocks progesterone receptors, the endometrium can no longer sustain the growing embryo. Without the effect of progesterone, the lining of the uterus breaks down, and bleeding begins. Mifepristone also triggers an increase in prostaglandin levels and dilates the cervix, facilitating abortion. Misoprostol then induces contractions of the smooth muscle fibers in the myometrium, relaxation of the uterine cervix and evacuation of intrauterine content.

Pharmacodynamics

Mifepristone

Mifepristone is a synthetic steroid with antiprogestational action as a result of competition at the progesterone receptors.

Mifepristone binds to human progesterone receptors with nanomolar affinity. In animals, oral administration was shown to inhibit the action of endogenous or exogenous progesterone in multiple species.

In women administered 1 mg/kg or greater, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction-inducing action of prostaglandins. During the first trimester, administration of mifepristone allows cervical dilatation.

In vitro studies showed mifepristone to also bind to the glucocorticoid and androgen receptors with high affinity, comparable to that for the progesterone receptor. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Misoprostol

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosage, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol facilitates cervical opening and evacuation of intrauterine content.

Pharmacokinetics

Mifepristone

Absorption:

After oral administration of a single dose of 200 mg, mifepristone is rapidly absorbed. The peak concentration of 2.3 to 2.7 mg/L is reached after 0.75 hours (mean of 49 subjects). The half-life of mifepristone is 36.5 to 38.3 hours.

The absolute bioavailability of a low oral dose of 20 mg is 69%.

Distribution: Mifepristone is 99% bound to plasma proteins, albumin and α1-acid glycoprotein in man. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Animal studies found mifepristone to be widely distributed, initially having high extravascular concentration, but shifting to greater erythrocyte concentration over 24 hrs. Studies in pregnant animals have shown mifepristone to cross the placental barrier.

Metabolism: Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. In vitro studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) N-monodemethylated metabolite, the most widely found in plasma; (2) N-didemethylated mifepristone, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11 ß; and (3) terminal hydroxylation of the 17-propynyl chain.

Excretion: Elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours. Mifepristone shows non-linear pharmacokinetics. Eleven days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for in the feces and 9% in the urine. Serum levels are undetectable at 11 days.

Misoprostol

Absorption: When administered orally, misoprostol is rapidly absorbed and metabolized. Peak concentrations around 1.1 ng/mL were reached about 15 minutes after a 400 microgram dose in the fasting state. Plasma concentrations of its main degradation metabolite, misoprostol acid, reach their peak of 2 - 2.5 ng/mL after a 2 microgram/kg oral dose within approximately 30 minutes and rapidly decline thereafter. As a result, uterine contractility increases and then plateaus after about one hour. Absorption is almost complete, measured at levels between 64 - 73% from urinary data. While not compared directly with oral administration, buccal administration has been found to result in peak concentrations comparable to those following vaginal administration, which have been found in turn to be lower and later than those for oral administration.

Distribution: Serum protein binding of labeled misoprostol acid was studied in man and was similar in young (81-88%) and elderly (81-89%) subjects. Accumulation in erythrocytes was not seen.

Metabolism: Metabolism of misoprostol to misoprostol acid is rapid with no intact misoprostol found in plasma consistent with an in vitro half-life of 6.4 minutes for the de-esterification of misoprostol in human plasma at 37ºC.

Excretion: Elimination of misoprostol and its metabolites is also rapid with a plasma elimination half-life of 21 minutes in man. 1-4% of misoprostol acid is excreted in the urine.

STORAGE AND STABILITY

Mifegymiso should be stored between 15-25°C in its original outer carton in order to protect from light. Keep out of the sight and reach of children.

Storage of mifepristone 200 mg tablet

When separated, mifepristone should be stored between 15-30°C; in the mifepristone (Green) box, in order to protect from light.

Storage of misoprostol 200 mcg tablets

When separated, misoprostol should be stored between 15-25°C; in the misoprostol (Orange) box.

SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Mifepristone 200 mg tablets

Mifepristone tablets are white to off white, round, biconvex with "MF" embossed on one side. Each tablet contains 200 mg of mifepristone and the following non-medicinal ingredients: colloidal silica anhydrous, magnesium stearate, maize starch, microcrystalline cellulose and povidone K30.

Mifepristone is packaged in a PVC/PVDC/Aluminum blister of 1 tablet presented in a green box of one tablet.

Misoprostol 200 mcg tablets

Misoprostol tablets are white, round flat with "ML" debossed on one side and "200" on the other side. Each tablet contains 200 mcg of misoprostol and the following non-medicinal ingredients: hydrogenated castor oil, hypromellose, microcrystalline cellulose and sodium starch glycolate.

Misoprostol tablets are packaged in dual-faced aluminum blisters and presented in an orange box of four (4) tablets.

The two products are provided in two different boxes which are packed together.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

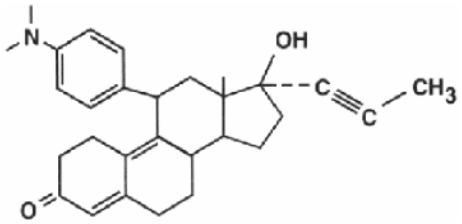
Mifepristone

Proper name or common name: mifepristone

Chemical name: (11β,17β)-11-[4-(Dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one
CAS Registry Number: 84371-65-3

Molecular formula and molecular mass: $C_{29}H_{35}NO_2$; 429.6 g/mol

Structural formula:



The absolute configuration of the chiral centers is as follows: 8S, 11R, 13S, 14S, 17R.

Physicochemical properties:

The compound is a yellow powder with a melting point of 191-196 °C. It is highly soluble in methanol and methylene chloride, and poorly soluble in water.

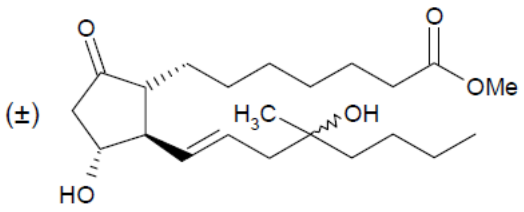
Misoprostol

Proper name or common name: misoprostol

Chemical name: (±)-Methyl (1R,2R,3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5- oxocyclopentaneheptanoate (USP)
CAS Registry Number: 59122-46-2

Molecular formula and molecular mass: $C_{22}H_{38}O_5$; 382.54g/mol

Structural formula:



The structure of misoprostol contains four chiral centers, the presence of 24 = 16 enantiomers is thus possible. Four of the 16 enantiomers comprise misoprostol [methyl (13E)-(±)-11,16- dihydroxy-16-methyl-9-oxoprost-13-en-1-oate], and the other 12 enantiomers comprise Impurity A (8-epi misoprostol), Impurity E (11-epi misoprostol) and Impurity B (12-epi misoprostol) by 4 enantiomers respectively.

Physicochemical properties:

Misoprostol is a clear, colorless to yellowish oily liquid. Practically insoluble in water, soluble in ethanol (96%), sparingly soluble in acetonitrile.

CLINICAL TRIALS

Study demographics and trial design

Study 1 (Middleton et al. 2005)[2]
This study was an open-label trial conducted in two family planning clinics in the United States. Healthy women (N = 152) with an intra-uterine pregnancy up to 49 days since the first day of the last menstrual period (LMP) verified by ultrasonography, requesting a termination of pregnancy received 200 mg oral mifepristone followed after 24 to 72 hours by 800 mcg buccal misoprostol. The efficacy of the procedure was assessed by vaginal ultrasound and adverse events were evaluated during a follow-up visit 4 to 15 days after mifepristone administration.

Study 2 (Winikoff et al. 2008)[3]
This open-label randomized seven-site study conducted in the United States compared the efficacy and safety of 200 mg oral mifepristone followed 24 to 36 hours later by 800 mcg buccal or oral misoprostol for early termination of pregnancy. Healthy women (N = 218) with an intra-uterine pregnancy up to 49 days LMP, determined by clinical examination and/or ultrasonography, were enrolled. The efficacy of the procedure was established by ultrasonography, and adverse events were assessed during a 7 to 14 days follow-up, after the intake of mifepristone.

Study 3 (Pena et al. 2014)[4]
This open-label single-arm study was conducted in three sites in Mexico. Its objective was to evaluate the safety and efficacy of mifepristone (200 mg oral) followed 24 to 48 hours by misoprostol (800 mcg buccal) for early pregnancy termination. Gestational age was determined by physical examination, menstrual history and ultrasound and 569 healthy women with pregnancy up to 49 days LMP were enrolled. Pregnancy termination was confirmed by

ultrasound and clinical exam 8 days after study enrollment.

Table 4: Summary of patient demographics for clinical trials in specific indication

Study Identifier	Study 1	Study 2	Study 3
Study Design	Open-label, randomized study	Open-label, randomized study	Open-label, single arm, prospective study
Study sites	2 family planning clinics (USA)	7 family planning clinics (USA)	2 secondary level hospitals and 1 primary care clinic (Mexico)
Patient enrolled	152 women with pregnancy ≤ 49 days LMP	218 women with pregnancy ≤ 49 days LMP	569 women with pregnancy ≤ 49 days LMP
Age	17 year or older	17 years or older	14 years or older
Mifepristone regimen	200 mg oral mifepristone	200 mg oral mifepristone	200 mg oral mifepristone
Mifepristone-misoprostol interval (hours)	24 to 72	24 to 36	24 to 48
Misoprostol regimen	800 mcg buccal misoprostol	800 mcg buccal misoprostol	800 mcg buccal misoprostol
Follow-up visit (Day post-mifepristone)	Day 4 to Day 15	Day 7 to Day 14	Day 8
Age ≤ 24 year old 25-29 year old 30-34 year old ≥ 35 year old	 52.8% 15.3% 19.4% 12.5%	 41.3% 27.2% 16.4% 15.0%	 51.6% 22.3% 13.8% 12.3%
Ethnicity African-American Asian Caucasian Hispanic Other	 26.9% 2.8% 63.4% 4.1% 2.8%	Not available	Not available
Gravidity 1 2-3 4+	 13.8% 46.1% 40.1%	 30.9% 33.8% 35.3%	 38.1% 44.3% 17.6%
Previous abortions	58.6%	47.6%	9.5%

Summary of clinical trial results

Results from the three phase 3 pivotal trials are summarized in Table 5 to Table 10. Clinical efficacy in the three pivotal trials was defined as complete abortion without surgical intervention. In the three studies, women presenting at follow-up with an on-going viable pregnancy were offered surgical termination of pregnancy. Ultrasound was performed in 97.9% of patients in clinical trials. Women presenting with a persistent gestational sac at first follow-up visit could opt for surgical intervention or wait and follow-up at a next visit for a spontaneous resolution on Day 15 to 36 post-mifepristone. In studies 2 and 3, women with a persistent gestational sac at the first follow-up visit could also choose to receive a second dose of 800 mcg buccal misoprostol. Of the 8 women choosing a second misoprostol dose, 7 had a complete abortion without surgery at next follow-up visit and 1 required a surgical intervention.

Table 5: Outcome of women undergoing medical termination of pregnancy

	Study		
	1 (N = 146)	2 (N = 214)	3 (N = 551)
Termination of pregnancy without surgical procedure	95.2%	97.3%	98.0%
Surgical termination of pregnancy:	4.8%	2.7%	2.0%
Indication for surgery: Persistent gestational sac	4.1%	0.9%	0%
Ongoing viable pregnancy	0.7%	0.9%	0.5%
Persistent heavy bleeding	-	0.9%	1.1%
Abdominal Pain	-	-	0.4%
Patient lost to follow-up	6	4	17

The results from the three trials indicate that a regimen of 200 mg oral mifepristone followed by 800 mcg buccal misoprostol is efficient for the termination of a pregnancy with a gestational age of 49 days or less. Stratification of the efficacy by age, ethnicity and gravidity status revealed no clinically meaningful difference in termination of pregnancy outcome.

Table 6: Total bleeding time from treatment by type of bleeding, in days: mean ± SD, median (range)*

	Study		
	1 (N = 143)	2 (N = 211)	3 (N = 551)
Total bleeding time	NA	10.8 ± 3.9, 11 (0-37)	NA
Heavy bleeding	2.3±2.3, 2 (0-15)	2.0±2.1, 2 (0-15)	NA
Normal bleeding	5.1±2.9, 5 (0-13)	4.3±2.8, 4 (0-15)	NA
Spotting	3.5±2.5, 3 (0-12)	4.6±3.2, 4 (0-14)	NA

One patient in Study 1 and one in Study 3 required a blood transfusion due to excessive bleeding.

Study results in women less than 18 years of age

Of the 551 women enrolled in Study 3, 35 were less than 18 years of age. The number of participants is stratified by age below:

Table 7: Number of participants <18 years, by age

Age <18	n
13	1
14	3
15	11
16	10
17	10
Total	35

In that population, all women (100 %) had termination of pregnancy without the need for a surgical intervention.

Table 8: Outcome of woman undergoing medical termination of pregnancy, by age

Age	Efficacy (n)
<18 years	100% (35)
≥18 years	98.0% (551)

Table 9: Reported pain and bleeding, by age

	< 18 years	**≥ 18 years**
Reported pain	(n=35)	(n=506)
Mean pain score (SD) (range 1-7)	5.60 (1.3)	5.06 (1.7)
Pain perception, %(n)*	(n=35)	(n=511)
Less than expected	11.4 (4)	28.4 (145)
Same as expected	22.9 (8)	26.2 (134)
More than expected	65.7 (23)	45.4 (232)
Bleeding perception, %(n)*	(n=35)	(n=510)
Less than expected	11.4 (4)	34.5 (176)
Same as expected	51.4 (18)	41 (209)
More than expected	37.1 (13)	24.5 (125)

*Excludes "Don't know" responses

Table 10: Adverse events by age

Side effect	< 18 years	≥ 18 years
Diarrhea	65.7%	58.6%
Nausea	34.3%	30.7%
Vomiting	42.9%	22.3%
Fever/chills	40%	44.3%
Headache	5.7%	12.3%
Dizziness	17.1%	13.1%
Weakness	17.1%	19.2%
None	0%	8.0%
Total (n)	35	551

Authorised Prescriber Program Study

This retrospective observational study conducted in 15 clinics in Australia reported the outcome of 4,488 patients having termination of pregnancy of less than 49 days since last menstrual period with a regimen of 200 mg mifepristone followed 24-48 hours later by 800 µg buccal misoprostol. In this study, 27 patients of less than 18 years of age were enrolled and all (100%) had a complete termination of pregnancy without surgery. There were no serious adverse events reported in this group.

Table 11: Number of participants <18 years in Australia Prescriber Program Study, by age

Age <18	n
13	0
14	0
15	1
16	8
17	18
Total	27

Australia Phase IV Study

This observational study conducted in women's health clinics in Australia reported the outcome of 8,165 patients having termination of pregnancy of 49 days since last menstrual period or less with a regimen of 200 mg mifepristone followed 24-48 hours later by 800 µg buccal misoprostol. In the study, 64 women of less than 18 years of age were enrolled and 62 (96.9%) had a complete termination of pregnancy without surgery. Two had an incomplete abortion requiring a surgical termination of pregnancy, a 15 and a 17 year old. No serious haemorrhage or infection was reported.

Table 12: Number of participants <18 years in Australian Phase IV Study, by age

Age <18	n
13	0
14	1
15	10
16	18
17	35
Total	64

DETAILED PHARMACOLOGY

Pharmacodynamics:

Mifepristone

Mifepristone is an orally active antiprogestogen which acts by competing with progesterone for receptor binding. It also possesses antiglucocorticoid and antiandrogenic activity. It is devoid of estrogenic, antiestrogenic, mineralocorticoid and antimineralocorticoid properties. Its ability to block the action of progesterone on the pregnant uterus provides a medical approach to termination of early pregnancy. In normally menstruating women, the effect of mifepristone depends on the timing of administration. When administered in the first half of the luteal phase, menstrual induction occurs independently of luteolysis; mifepristone administration during the mid-luteal phase produced bleeding within a few days in most women but there was a second bleed at the time of expected menses in about two-thirds. The first episode of bleeding occurred in the presence of elevated progesterone and estrogen concentrations. Administration during the late luteal phase resulted in bleeding within 1 to 3 days, shortening the luteal phase of the treatment cycle and lengthening of the subsequent follicular phase. Administration on the first 3 days of the menstrual cycle had no effect on cycle length but when given in the late follicular phase, mifepristone prolonged the follicular phase by preventing the development of a normal LH surge and delaying the new surge for about 15 days.

In the first trimester of pregnancy, mifepristone induced uterine activity in virtually all women 36 and 48 hours after administration, and increased the sensitivity of myometrium to exogenous prostaglandins (PG). The accompanying increase in decidual $PGF_{2\alpha}$ production was attenuated by indomethacin, but the increase in uterine activity was not: thus, mechanisms other than an increase in decidual PG production contribute to the abortifacient effect of mifepristone. Mifepristone administration also resulted in cervical ripening in pregnant women.

Single doses of mifepristone of 4.5 and 6 mg/kg increase plasma levels of cortisol, ACTH and lipotrophin, and in patients with unresectable meningioma treated with 200 mg mifepristone daily for prolonged periods, increases in plasma cortisol, ACTH and urinary cortisol are maximal at 3 weeks and remain unchanged thereafter. Dosages of mifepristone required to exert antiglucocorticoid effects, which are achieved by disruption of the negative pituitary feedback, are higher than those needed for antiprogestogen activity. In subjects with normal adrenal function, the increase in ACTH produced by mifepristone compensates for its antiglucocorticoid activity and there have been no reports of acute adrenal insufficiency at dosages used to terminate

early pregnancy.

Mifepristone inhibited estrous cycling in rats at oral doses of 0.3-1 mg/kg/day (less than the clinical dose adjusted for body surface area) in a 3-week study. This was reversed over the following 2-3 weeks and no subsequent effects on reproductive performance were found.

In fertility studies in rats in which treated females were mated with treated males, increased pre-implantation losses were observed with misoprostol at oral doses greater than 1 mg/kg/day (11 times the recommended human dose, on a mg/m^2 basis). Post-implantation loss was also increased at 10 mg/kg/day (114 times the recommended human dose, on a mg/m^2 basis).

Misoprostol

Misoprostol is a synthetic analogue of prostaglandin E1. At the recommended dosages, misoprostol induces contractions of the smooth muscle fibers in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of intrauterine content. In the event of an early termination of pregnancy, the combination of misoprostol used in a sequential regimen after mifepristone leads to an increase in the success rate and accelerates the expulsion of the conceptus. Among other effects, misoprostol inhibits the acid gastric secretion and increases the digestive peristaltism.

Uterine contractility following administration of misoprostol via the buccal route was investigated with an intrauterine pressure transducer in women seeking termination of pregnancy. Results indicated that the average time to onset of increased tone and first uterine contraction were 41.2 and 67.1 minutes, respectively. Sustained uterine activity was observed on average after 90.0 minutes and peak uterine activity after 264.0 minutes.[5]

Pharmacokinetics:

Mifepristone

The pharmacokinetic properties of mifepristone have been studied mostly following oral administration in healthy women, although studies were also conducted in pregnant women and a few male volunteers. Plasma concentrations of mifepristone and its metabolites were measured by radioimmuno- and radioreceptor assays, or high performance liquid chromatography (HPLC), and pharmacokinetic parameters calculated employing one- and two-compartment models as well as non-compartmental analysis.

The pharmacokinetics of mifepristone and its metabolites are not linear. Following oral administration of single doses of mifepristone 100, 400, 600 and 800 mg to healthy female volunteers maximum plasma concentrations were about 2.5 mg/L (2500 ng/mL) and differed between the 100 and 800 mg doses only 2 hours after ingestion. After a single 600 mg dose maximum plasma concentration was about 2 mg/L (2000 ng/mL) at 1.35 hours. High doses of 10 and 25 mg/kg in healthy female and male volunteers produced maximum plasma concentrations of progesterone receptor-reactive material of 5.17 to 7.5 mg/L. Maximum plasma concentrations were attained 0.7 to 1.5 hours after oral administration. The parent drug and its metabolites were still detectable 6 to 7 days after a single dose using HPLC and for 10 days using radioimmunoassay.

Administration of 12.5, 25, 50 or 100 mg twice daily for 4 days to healthy female volunteers resulted in similar plasma concentrations of 1.4 to1.7 mg/L (1400 to 1700 ng/mL) at dosages $\geq$ 50 mg twice daily, and it was suggested that the lack of increase in plasma drug concentration when dosage increased above 50 mg twice daily is partly explained by saturation of α-I-acid glycoprotein (AAG), the serum binding protein for mifepristone in man, which has a binding capacity lower than the therapeutic dose.

Plasma concentration and clinical efficacy: a study conducted in 17 women less than 56 days pregnant who were administered mifepristone 600 mg for termination of pregnancy, found no correlation between clinical efficacy (13 responders) and plasma concentration of mifepristone or circulating metabolites, protein binding, or plasma AAG.

Blood distribution and binding to plasma proteins:

Apparent initial volume of distribution after intravenous administration of mifepristone 280 mg was low (8 L) but at steady state was 25.7 L. The volume of distribution and clearance of mifepristone were inversely proportional to the plasma concentration of AAG, being greater in subjects with low AAG levels, and are dose· and time-dependent. At plasma concentrations of up to 0.8 mg/L mifepristone is about 98 % bound to plasma proteins in the blood. Its binding to erythrocytes is negligible. A value of 94 % was reported at a plasma mifepristone concentration of 5 mg/L. It is considered that AAG is the principal binding protein for mifepristone. When binding to AAG is saturated, mifepristone and its metabolites bind to albumin.

Absolute bioavailability:

Absolute bioavailability after a dose of 20 mg mifepristone is 69 %.

Metabolism:

After oral administration, mifepristone is metabolized to N-mono and dimethylated as well as hydroxylated compounds. The three measurable metabolites are: N- monodemethylated mifepristone, terminal hydroxylation of the 17-propynyl chain, and N-didemethylated mifepristone. All three metabolites are found in rats and cynomolgus monkeys. Metabolites are detectable in plasma 1 hour after ingestion of mifepristone. Their concentrations increase dose-dependently with those of the monodemethylated metabolite sometimes exceeding those of the parent compound. The plasma concentrations of the didemethylated compound rises gradually over the first 10 hours following mifepristone administration. The binding affinity of the metabolites to progesterone receptors is about 10 to 20% of that of mifepristone and it is not known whether they contribute to the pharmacological effects of mifepristone.

Effect of CYP3A4 on the oxidation of mifepristone in human liver microsomes:

Using *in vitro* techniques, it has been demonstrated[6] that human liver microsomes catalyzed the demethylation of mifepristone with mean ($\pm$ SD) apparent K_m and V_{max} values of 10.6 $\pm$ 3.8 μM and 4920 $\pm$ 1340 pmol/min/mg protein. CYP3A4 substrates progesterone and midazolam inhibited metabolite formation by up to 77 %. Other isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2E1) had apparently no action on mifepristone metabolism. CYP3A4 appears as the

isoenzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes.

Excretion:

Total plasma clearance of mifepristone was reported to be 3 L/h. Following oral administration of tritiated mifepristone to healthy volunteers, 90% of the dose was recovered in the feces over a period of 6 to7 days. As mifepristone was completely absorbed, the principal route of elimination was biliary. The urinary route was secondary and renal clearance was negligible relative to total clearance.

In studies employing long sampling periods, the elimination half-life of mifepristone was reported to be 24 to 54 hours.

Misoprostol

After oral administration, misoprostol is rapidly absorbed (Tmax: 30 minutes) and converted to its pharmacologically active metabolite, misoprostol acid. Its plasma half life is 1.5 hrs. After administration of radio-labeled misoprostol, approximately 80% of radioactive products are eliminated in the urine and feces, respectively[7]. Approximately 56 % of the product is eliminated in the urine within 8 hours after intake.

Overall, areas under curve tend to be higher when misoprostol is administered via vaginal, sublingual or buccal routes when compared to oral administration. A study[8] compared the pharmacokinetics of misoprostol (800 µg) administered either sublingually or buccally in non pregnant women: misoprostol plasma concentrations were higher for the sublingual vs. the buccal route. The misoprostol $AUC_{0-\infty}$ (1910 vs. 484 pg/mL, sublingual and buccal, respectively, $p<0.04$) and AUC_{0-4h} (1600 vs. 380 pg/mL, sublingual and buccal, respectively, $p<0.03$) were lower when given by the buccal route. Sublingual misoprostol administration achieved a higher Cmax compared to buccal (1140 vs. 229 pg/mL, $p<0.03$). No difference was found when comparing sublingual and buccal Cmin or half-life.

A bioequivalence study has been performed comparing oral misoprostol (200 mcg tablet) to oral Cytotec® (200 mcg tablet); this study has demonstrated the detailed pharmacokinetics of misoprostol.

As anticipated in the study protocol, parametric confidence intervals were used for the evaluation of the relative bioavailability as the ANOVA residuals did not deviate from normal distribution. The following formal preconditions for the evaluation of the relative bioavailability were checked and found to be met.

A terminal elimination half-life of < 2.5 h was observed in all subjects. The wash-out phase of at least 1 week was adequate, corresponding to at least 60 times the apparent terminal disposition half-life in the subjects. A carry over from one treatment to the other thus was methodologically excluded by an adequate wash-out. The ANOVA revealed, correspondingly no significant sequence effect for any of the pharmacokinetic characteristics. Also no period effect occurred.
An adequate portion of the total area under the curve of >80% was covered by measured concentrations in all subjects.

The 90% confidence intervals of the AUC_{0-t} ratio (89.4-101%), $AUC_{0-\infty}$ ratio (90.4- 102%) and Cmax ratio (83.4-105%) were included by the acceptance range of 80- 125%.

	Mean	Median	SD	Q1	Q3
$AUC_{0\ t}$ (h·ng/mL)	0.710	0.650	0.247	0.523	0.862
AUC_0 (h·ng/mL)	0.746	0.674	0.259	0.545	0.918
C_{max} (ng/mL)	1.10	1.07	0.42	0.871	1.28
MRT (h)	0.776	0.690	0.428	0.589	0.764
T_{max} (h)	0.246	0.250	0.129	0.167	0.333
$T_{1/2}$ (h)	0.581	0.476	0.444	0.379	0.524

MICROBIOLOGY

Not applicable; mifepristone 200 mg tablet and misoprostol 200 mcg tablets are not sterile.

TOXICOLOGY

Single dose studies

Mifepristone
Mice, rats and dogs were administered single p.o. and i.p. doses of 1000 mg/kg of mifepristone, resulting in severe toxicities (arched back, locomotor problems and abdominal distension) and one animal died. The drug dose used in these studies was about 300 fold greater (on a mg/kg basis) than would be administered to patients.

Misoprostol
Studies were performed in mice, rats and dogs. Oral LD50 values in mice and rats were 27-138 and 81-100 mg/kg, respectively, with corresponding values after i.p. dosing of 70-160 and 40-62 mg/kg. No deaths were reported in dogs up to 10 mg/kg, the maximum administered dose. The most prominent clinical signs were diarrhea and reduced motor activity in rodents and, in dogs, emesis, tremors, mydriasis and diarrhea. Most deaths occurred within 24 hours of dosing and surviving animals appeared normal within 3-4 days. The drug dose used in these studies was at least >750 fold greater (on an mg/kg basis) than would be administered to patients.

Long term studies

Mifepristone
Repeat dose toxicology studies were conducted in the rat and the monkey for 30 days and 6 months. A range of doses from 5 – 200 mg/kg/day were used.

Monkeys administered 100 mg/kg/day had severe toxicity, where 3 were sacrificed moribund and the primary toxicological effects were vomiting, diarrhea, reduced appetite and body weight loss. Mid and high dose animals had reduced food consumption and loss of body weight. Serum ACTH levels were increased, cholesterol reduced, triglycerides had a transient rise and cortisol was increased. Both progesterone and estrogen levels were lower and LH levels were higher in females. Urinary excretion of potassium and chloride was reduced at all dose levels and sodium only at the high dose. In both sexes, kidney and adrenal weights were increased at all dose levels, liver weights were increased at the mid- and high-dose and pancreas reduced at the high-dose. Histopathology showed (i) non dose-related increased amounts and incidence of lipofucsin in liver, (ii) non dose-related increase in cortical scarring, cortical cysts and subcapsular foci of fibrosis in kidneys, (iii) increased eosinophilia of adrenal zona fasciculata in high-dose males and females and in one mid-dose male; high-dose females had an increased width of the zona reticularis, and (iv) increased incidence of brown pigment within the thyroid follicular epithelium in high-dose animals.

With regard to changes in reproductive organs in female monkeys, the following observations were made: (i) dilated ovarian follicles and an absence of corpora lutea, (ii) thinning of uterine endometrium; focal mucosal hyperplasia, squamous metaplasia and inflammatory cell infiltration (iii) non dose-related squamous metaplasia and inflammatory cell infiltration in the cervix, (iv) moderately keratinised vagina, (v) dilated lumen of fallopian tubes, (vi) slight increase in the degree of development of mammary glands.

Rats administered mid and high doses had reduced weight gain. Haematological measures showed reduced red cell parameters and reduced clotting time. Plasma glucose was dose-dependently reduced and serum protein and cholesterol increased. Urinalysis showed increased protein and increased urine volume, presumably due to increased water intake. Histopathology showed (i) dose-related increase in centrilobular enlargement in livers, (ii) dose-related increase in hemosideresis in adrenals, (iii) dose-related increase in foci of basophilic/dilated kidney tubules containing colloid, glomerular hyalinisation/sclerosis, and interstitial fibrosis (iv) increased thyroid weight, increased height of the thyroid follicular epithelium; a thyroid follicular adenoma was observed in one high-dose female.

With regard to changes in reproductive organs in female rats, the following observations were made: (i) inhibition of oestrus cyclicity and reduction in corpora lutea, (ii) dose-related increase in ovarian cysts, (iii) reduction in endometrial stroma in all groups and dose-related dilatation of endometrial glands, (iv) striated squamous epithelium of the cervix/vagina, and (v) dose-related increase in distension of mammary acini and ducts.

The Cmax of single-dose oral mifepristone administration in rats and monkeys was compared to the Cmax in women administered 200 mg. Rats and monkeys were observed to have different mifepristone metabolism, as compared to humans, making it challenging to compare the doses used in animal studies to those proposed for human use.

	Dose (mg/kg)	Cmax (ng/ml)	Cmax:Dose
Rat	200	3000	15
Monkey	90	160	1.7
Human	4	2686	671.5

Misoprostol
Repeat dose studies were conducted in rats and dog for 5, 13 and 52 weeks and covered a dose range of 30 – 9000 mcg/kg/day.

In rats, the major clinical signs were diarrhea, salivation, vaginal dilation and discharge, decreased body weight and increased food consumption. Principal clinical biochemistry changes were decreases in serum total protein and increases in serum iron, with any changes in other parameters remaining within normal limits and considered incidental. The decrease in protein levels may be a consequence of poor absorption of nutrients resulting from diarrhea. Stomach weights and stomach to body weight ratios were increased and hyperkeratosis of the aglandular part of the stomach and mucosal epithelial hyperplasia of the glandular part were confirmed by electron microscopy. It may be that misoprostol increased cell survival and decreased cell shedding. The changes were reversible upon cessation of treatment.

Pharmacokinetic exposure data for misoprostol was limited, making it challenging to compare the doses used in animal studies to those proposed for human use.

Reproductive and developmental studies

Mifepristone
Administration of mifepristone to rats disrupted the oestrus cycle at both dose levels, 0.3 and 1 mg/kg/day within 10 days of treatment, with a gradual restoration of the cycle over the 2-3 weeks after stopping dosing. There were no residual effects on reproductive performance, fertility or the wellbeing of offspring.

When administered to at a dose of 2.5 mg/kg/day for 24 days, starting 8 days before mating, with pregnancy status assessed on the day after final treatment, mifepristone did not affect the pregnancy rate, as compared to a concurrent control group. However, the mean number of normal implantation sites per pregnant rate was significantly reduced.

Mifepristone is embryotoxic and its administration to pregnant mice, rats and rabbits at doses lower than those proposed for human use (on a mg/kg basis) resulted in fetal loss.

There were fetal anomalies reported in rabbits following mifepristone exposure of the dams during pregnancy: failure of closure of the cranium and haemorrhagic destruction of the upper part of the head or brain, no spinal column, no closure of the eyelids, exencephaly, interventricular communication in the heart, cleft palate, generalised eczema and celosomia. In monkeys embryos exposed to mifepristone showed compromised developmental potential. These anomalies may be a consequence of progesterone withdrawal, as progesterone is needed to maintain uterine accommodation during pregnancy, rather than direct teratogenic effect.

In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth resulted in delays in the development of the righting reflex and the responses in the rotarod and water maze tests in pups. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. However, reproductive function in males or females was normal.

In a separate study neonatal rats received 1 mg of mifepristone every second day from day 1 to day 15 or day 4 to day 18 of life. Female rats developed abnormalities of the oviduct and ovarian capsule and during adulthood anovulatory polyfollicular ovaries developed. Males showed retardation of testicular growth and delay of puberty. Sexual behaviour in adulthood was deficient in that ejaculations only rarely occurred; when they did occur, however, fertility was unimpaired. Adrenal gland development was also impacted but this recovered after the cessation of treatment whereas the effects on reproduction continued into adulthood.

Misoprostol
The effect of misoprostol on female cyclicity, mating and fertility was not studied.

In two fertility studies, female rats were administered misoprostol from 15 days premating to parturition and from 14 days premating to day 7 of gestation. The number of implantations was decreased at 1600 and 10000 µg/kg/day and an increase in resorptions occurred at 1000 and 10000 µg/kg/day. As a consequence, there were a decreased number of live foetuses or pups at 10000 µg/kg/day and a decreased number of foetuses at 1600 µg/kg/day. Foetal and pup survival and development were not affected.

In two teratology studies in rats pregnant dams were dosed on days 6 to 15 or 7 to 17 of gestation up to 10000 ug/kg/day; there was no evidence of embryotoxicity, foetotoxicity or teratogenicity. Two rabbit studies used doses up to 1000 µg/kg/day on days 6 to 18 of gestation and also showed no evidence of foetotoxicity or teratogenicity, although there was an increased number of resorptions at 1000 µg/kg/day in one study.

However, a more recent study in mice treated with single doses of 20 or 30 mg/kg of misoprostol on day 10 of pregnancy showed an increase in resorptions at 30 mg/kg and an increased occurrence of cleft palate as well as other skeletal abnormalities in surviving fetuses. The link between misoprostol exposure during pregnancy and congenital malformations might be attributed to disturbances in blood supply to the foetus.

A retrospective analysis of human data also determined there to be a link between misoprostol exposure during pregnancy and congenital malformation.

Carcinogenesis and Mutagenesis

Mifepristone
Mifepristone was tested for genotoxicity using both in vitro and in vivo studies. It showed no evidence of genotoxicity and carcinogenicity studies were not conducted.

Misoprostol
Misoprostol was tested for genotoxicity using both in vitro and in vivo studies and showed no evidence of genotoxicity. The carcinogenicity potential of misoprostol has been evaluated in both mice and rats. There was no indication of a carcinogenic effect in either species.

Phototoxicity

Mifepristone
No evidence of phototoxicity was observed with mifepristone being tested up to a concentration of 8 µg/mL in Balb/c 3T3 fibroblasts, the limit of solubility under the conditions of the assay.

REFERENCES

1 Bernard N., Elefant E., Cartier P., Tebacher M., Barjhoux CE., Bos-Thompson MA. et al. Continuation of pregnancy after first-trimester exposure to mifepristone : an observational prospective study. Br. J. Obstet Gynecol 2013, 120: 568-575.

2 Middleton T., Schaff E., Fielding SL., Scahill M., Shannon C., Westheimer E., Wilkinson T. and Winikoff B. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005, 72:328-332

3 Winikoff B., Dzuba IG., Creinin MD., Crowden WA., Goldberg AB., Gonzales J. et al. Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion. ARandomized Controlled Trial. Obstetr Gynecol 2008, 112: 1303-1310

4 Pena M., Dzuba IG., Smith PS., Mendoza LJA., Bousi/guez M., Martinez MLG. et al. Efficacy and acceptability of a mifepristone-misoprostol combined regimen for early induced abortion amoung women in Mexico City. Int.J. Gynaecol Obstet 2014, 127:82-85

5 Meckstroth KR, Whitaker AK, Bertisch S, Goldberg AB, Darney PD. Misoprotol administered by epithelial routes: Drug absorption and uterine response. Obstetr Gynecol 2006, 108, 582-90.

6 Jang G.R., Wrigton and Benet L.Z. Identification of CYP3A4 as the principal enzyme catalazing mifepristone (RU 486) oxidation in human liver microsomes. Biochem Pharmacol 1996; 52, 753-61

7 Collins PW. Misoprostol: discovery, development and clinical applications. Med Res Rev. 1990 10, 149-72.

8 Schaff EA, DiCenzo R, Fielding SL. Comparison of misoprostol plasma concentrations following buccal and sublingual administration. Contraception 2005, 71, 22-5.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

MIFEGYMISO

Mifepristone tablet/Misoprostol tablets

Read this carefully before you start taking **Mifegymiso**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Mifegymiso**.

Serious Warnings and Precautions

Follow-up appointment:
You must see a doctor, 7 to 14 days after Step 1 (taking the mifepristone tablet from the green box). The doctor will check whether your pregnancy has completely ended. If the pregnancy continues, there is a possibility of birth defects. Your doctor will talk with you about your options.

Risk of infection and sepsis:
If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your doctor without delay. Very rarely, this can cause death.

Prolonged heavy bleeding:
Contact a doctor right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours. Bleeding can be so heavy that it requires a surgical procedure. Some patients also require a blood transfusion.

Risks of birth defects:
Once you start Mifegymiso, you should complete both steps. Both Mifepristone and Misoprostol can cause birth defects if your pregnancy is continued.

If you do NOT want to get pregnant after the termination of your pregnancy:
You must start using birth control right away.

You can get pregnant right after the abortion:
If you want to have a baby, tell your doctor. To decrease the chance of birth defects, avoid getting pregnant again before your next period. This will protect the baby from any exposure to Mifegymiso. Use birth control during this one month waiting period.

What is Mifegymiso used for?

Mifegymiso is used for ending your pregnancy. This is called an abortion. Mifegymiso is only used if your last period started 49 days ago or less.

How does Mifegymiso work?

Do NOT use Mifegymiso as birth control.

Before you get Mifegymiso:

- Your doctor will require that you sign a consent form and the Patient Information Card
- Your doctor must complete mandatory education and registration programs
- You will get counselling. Your healthcare professional will tell you about the chance of:
    - Bleeding
    - Infection
    - An incomplete abortion
    - How to access the treatment centre by telephone or local access
- You will get a printed copy of the Mifegymiso Patient Medication Information document and Patient Information Card.

Patient Information Card
The doctor will give you a Patient Information Card. Both you and the doctor must sign this card. Your signatures show that you have read the Patient Medication Information document.

Keep this card with you at all times while taking Mifegymiso until your doctor tells you that your abortion is compete.

It contains the following information:

- Your follow-up appointment location, date, and time
- Contact information in case you need to call the doctor or clinic
- Location of where you should go if you have an emergency
- Manufacturer's 24 hour support line 1-877-230-4227. Call this number if you need assistance but you cannot reach your own doctor or clinic.

Show this Card to your emergency healthcare professional.

To end your pregnancy, you will need to take two drugs.

Step 1 (Green Box)
Mifepristone is taken first to block a hormone that is needed for your pregnancy to continue.

Step 2 (Orange Box)
Misoprostol is the second drug. It is taken 24-48 hours later. It causes the uterus to contract and relaxes the opening of the cervix.

Vaginal bleeding usually starts a few hours after taking the Misoprostol tablets.

Cramping and vaginal bleeding are normal with this treatment. Usually, this indicates that the treatment is working. Bleeding lasts for an average of 11 days. It is usual for bleeding to be heavier than a normal period for 2 to 3 days.

You may see blood clots and tissue. This is an expected part of ending the pregnancy.

What are the ingredients in Mifegymiso?

Medicinal ingredients:
Green box: Mifepristone
Orange box: Misoprostol

Non-medicinal ingredients:
Mifepristone (green box): colloidal silica anhydrous, magnesium stearate, maize starch, microcrystalline cellulose, povidone K30

Misoprostol (orange box): hydrogenated castor oil, hypromellose, microcrystalline cellulose, sodium starch glycolate

Mifegymiso comes in the following dosage forms:

Green box: 1 Mifepristone tablet, 200 mg for oral use

Orange box: 4 Misoprostol tablets, 200 mcg each (800 mcg total) for buccal use

Do not use Mifegymiso if:
- You are pregnant and wish to carry your pregnancy to term
- You do NOT have access to emergency medical care. You must be able to get medical help in the 14 days after you take the mifepristone tablet
- You have an ectopic pregnancy (the egg is implanted outside the womb)
- You are using an intrauterine contraceptive device (IUD) in your uterus
- You have not had an ultrasound scan
- The duration of your pregnancy is uncertain
- You have any allergies to mifepristone, misoprostol or any of the other ingredients listed in this leaflet
- You have a chronic adrenal disease
- You take corticosteroids on a regular basis
- You have a bleeding problem
- You take a blood thinner (anticoagulant like coumadin)
- You have inherited porphyria. This is a blood disease that causes skin symptoms as a result of oversensitivity to sunlight
- You have uncontrolled asthma

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Mifegymiso. Talk about any health conditions or problems you may have, including if you:
- Have kidney problems
- Have liver problems
- Are underweight
- Have problems with your adrenal glands
- Have a heart or cardiovascular disease
- Have anemia (problems of red blood cells)

- Have asthma
- Have had seizures
- Are taking medications (corticosteroids) for the treatment of asthma
- Are diabetic
- Are a heavy smoker and over 35 years old

Other warnings you should know about:

If your blood group is negative (A^-, B^-, AB^-, O^-), your doctor will give you an additional medication prior to giving you **Mifegymiso**.

Mifegymiso does not work in 2% to 4.8% of cases. If this happens to you, you will need a surgical abortion.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Mifegymiso:
- Drugs used in the treatment of fungal infection such as ketoconazole, itraconazole
- Antibacterial named erythromycin
- Antibiotic used in the treatment of tuberculosis named rifampin
- Certain anticonvulsants used to treat epilepsy, such as phenytoin, phenobarbital and carbamazepine
- Corticosteroids
- Herbal supplements containing St. John's Wort
- Grapefruit juice
- Some drugs used for general anaesthesia.

How to take Mifegymiso and Usual dose:

While you are bleeding, plan to stay near the doctor or clinic. That way you can call or visit them if necessary.

Mifegymiso contains two drugs. You must take both to terminate your pregnancy.

Take **Mifegymiso**
- As directed by your doctor or as given to you by medical staff

Step 1:
As directed by your doctor or a member of the medical staff:

(Green box)
Take the Mifepristone tablet
- Swallow tablet with a glass of water

24 to 48 hours after taking the Mifepristone tablet, you must do Step 2.

Step 2:

(Orange box)

- Place the 4 Misoprostol tablets (as a single 800 mcg buccal dose) in your mouth
- Keep the 4 tablets between your cheeks and gums for 30 minutes
- Then, swallow any fragments that are left with water

Plan to rest for 3 hours after taking the Misoprostol tablets.

Overdose:

If you think you have taken too much **Mifegymiso**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Contact your doctor immediately if you forget to take the dose of Misoprostol tablets (Step 2) and it is more than 48 hours after you have taken the Mifepristone tablet (Step 1).

What are possible side effects from using Mifegymiso?

These are not all the possible side effects you may feel when taking **Mifegymiso**. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Side effects may include:

- breast tenderness
- hot flushes, chills
- nausea, vomiting
- diarrhea
- dizziness, headache, fainting
- fatigue

These side effects slow down after Day 3 and are usually gone by Day 14. Your doctor will tell you how to manage any pain or other side effects.

Mifegymiso can cause abnormal blood test results. Your doctor will decide when to perform tests and interpret the results.

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
COMMON **Prolonged heavy bleeding** **Severe hemorrhage:** you bleed enough to soak through two full-size sanitary pads per hour for two consecutive hours.			√ √
Fever			√
Endometritis (an infection in the lining of the uterus): Pain in the lower abdomen. Fever and abnormal vaginal discharge and bleeding.			√
UNCOMMON **Hemorrhagic shock** (shock from blood loss): Dizziness and confusion. Rapid breathing and heartbeat. Weakness, low blood pressure, less urine than normal Cool clammy skin, thirst and dry mouth.			√
Hypotension (low blood pressure): dizziness, fainting, lightheadedness	√		
Infection: 24 hours or more after Step 2, fever, chills and abdominal pain, cramps or tenderness that persist for 4 hours with or without nausea, vomiting, diarrhea, weakness, rapid heartbeat or feel unwell.			√
Skin rash: Red spots on your skin			√
RARE **Anaphylactic shock or Angioedema** (serious allergic reaction): Itching, rash, hives. Swelling of the face, lips, tongue or throat. Difficulty swallowing or breathing.			√

Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
Toxic shock syndrome (life-threatening infection): Fever, diarrhea, nausea, vomiting, muscle aches. Low blood pressure, headache, confusion and seizures. Rash or red spots that look like a sun burn. Redness of the eyes, mouth and throat.			√
Asthma or bronchospasm: Difficulty breathing and coughing. Whistling sound when you breath. Chest tightness and mucus in your lungs.			√
Severe Skin Reaction: **Urticarial reaction**: Skin with red spots which burn, itch or sting. **Toxic epidermal necrolysis:** Severe skin peeling, especially in mouth and eyes **Erythema nodosum** (swelling of the fat cells under the skin): Tender red lumps usually on both shins.			√ √ √

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:
- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep out of sight and reach of children.
Do not use after any expiry date printed on the boxes, or if the boxes are damaged.

Storage of Mifegymiso
Store entire package between 15-25°C in its original box in order to protect from light.

Storage of mifepristone 200 mg tablet
When separated, mifepristone should be stored in the green box between 15-30°C, in order to protect from light.

Storage of misoprostol 200 mcg tablets
When separated, misoprostol should be stored in the orange box between 15-25°C.

If you want more information about Mifegymiso:
- Talk to your doctor
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website, or by calling 1-877-230-4227.

This leaflet was prepared by Linepharma International Limited.

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