

# MTP Kit (Mifepristone + Misoprostol)

For the use of Gynaecologists only

## Warning

**Product is to be used only under the supervision of a service provider and in a medical facility as specified under MTP Act 2002 and MTP Rules 2003.**

## Qualitative and Quantitative Composition

Each pack contains 5 tablets:

A. 1 Mifepristone Tablet

Each uncoated tablet contains:

Mifepristone...200 mg

B. 4 Misoprostol Tablets

Each uncoated tablet contains:

Misoprostol...200 mcg

## Dosage Form and Strength

Mifepristone tablet for oral use and misoprostol tablets for vaginal use.

## Clinical Particulars

### Therapeutic Indication

**MTP Kit** is indicated for the medical termination of intrauterine pregnancy of up to 63 days gestation based on the first day of the last menstrual period.

### Posology and Method of Administration

**MTP Kit** is indicated for the medical termination of intrauterine pregnancy of up to **63 days** of gestation. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed **28-day** cycle with ovulation occurring at mid-cycle.

The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device (IUD) should be removed before treatment with mifepristone and

misoprostol begins. Pregnancy termination by surgery is recommended in cases when **MTP Kit** fails to cause termination of intrauterine pregnancy.

Mifepristone may be administered by or under the supervision of a Gynaecologist, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. The Gynaecologist must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure the patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

The dosage is mifepristone 200 mg orally followed 1 - 3 days later by misoprostol 800 mcg (4 tablets of 200 mcg) vaginally. The misoprostol may be administered by a health care provider or self-administered by the woman. For women at 49 - 63 days of gestation, if abortion has not occurred 4 hours after administration of misoprostol, a second dose of misoprostol 400 mcg (2 tablets of 200 mcg) may be administered vaginally or orally (depending upon preference and amount of bleeding).

The patient should return for a follow-up visit approximately 14 days after the administration of mifepristone. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

**Patients who have an ongoing pregnancy at this visit have a risk of foetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures.**

## **Contraindications**

Administration of mifepristone and misoprostol for the termination of pregnancy (the 'treatment procedure') is contraindicated in patients with any one of the following conditions:

- History of allergy or known hypersensitivity to mifepristone, misoprostol or other prostaglandin (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported)
- Confirmed or suspected extra-uterine / ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy)
- IUD in place (the IUD might interfere with pregnancy termination)
- Chronic adrenal failure (risk of acute renal insufficiency)
- Haemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)
- Inherited porphyrias (risk of worsening or of precipitation of attacks)
- Concurrent long-term corticosteroid therapy (risk of acute renal insufficiency)
- Severe asthma uncontrolled by therapy
- Pregnancy not confirmed by gynaecological examination, ultrasound scan or biological tests
- Pregnancy beyond 63 days of amenorrhoea

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering health care provider.

Mifepristone also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen.

## **Special Warnings and Precautions for Use**

## ***General***

In the absence of specific studies, mifepristone is not recommended in patients with:

- Renal failure
- Hepatic failure
- Malnutrition

The administration of mifepristone must be under the supervision of a qualified Gynaecologist.

The use of mifepristone is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease; insulin-dependent diabetes mellitus; severe anaemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of mifepristone may be lower if misoprostol is administered more than 2 days after mifepristone administration.

Patients with prosthetic heart valves or who have had one previous episode of infective endocarditis should receive appropriate prophylactic antibiotic treatment.

A physical examination must be performed by a qualified trained medical professional in a woman who has undergone genital mutilation to exclude any anatomical obstacles to medical abortion.

During clinical trials, pregnancies occurred between embryo expulsion (abortion) and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that unprotected sexual intercourse be avoided until the appearance of the first menses after the abortion. Reliable contraception should commence as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

## ***Information for Patients***

Patients should be fully advised of the treatment procedure and its effects. Each patient must understand:

- the necessity to combine treatment with prostaglandin to be administered at a second visit, 1 to 3 days after administration of mifepristone
- the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking mifepristone in order to check for complete expulsion
- that vaginal bleeding and uterine cramping probably will occur
- that prolonged heavy vaginal bleeding is not proof of a complete abortion
- that if the treatment fails, there is a risk of foetal malformation
- that medical abortion treatment failures are managed by surgical termination
- the steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns

## ***Laboratory Tests***

Clinical examination is necessary to confirm the complete termination of pregnancy after the

treatment procedure. Changes in quantitative human chorionic gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of mifepristone. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in haemoglobin concentration, haematocrit and red blood cell count occur in some women who bleed heavily. Haemoglobin decreases of more than 2 g/dL occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], alkaline phosphatase, gamma-glutamyltransferase [GT]) activities were rarely reported.

### ***Precautions for Use***

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1mg of dexamethasone antagonizes a dose of 400mg of mifepristone.

Due to the anti-glucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of mifepristone. Therapy should be adjusted.

A decrease of the efficacy of the method can theoretically occur due to the anti-prostaglandin properties of nonsteroidal 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 and does not reduce the clinical efficacy of medical termination of pregnancy.

Rare but serious cardiovascular accidents have been reported following the intramuscular administration of prostaglandin analogue. For this reason, women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

### ***Serious Adverse Events***

Patients must be monitored and undergo appropriate medical evaluation and intervention should any of the serious adverse events mentioned below occur following a spontaneous, surgical or medical abortion, including following mifepristone use:

#### ***Uterine / Vaginal Bleeding***

Uterine / vaginal bleeding occurs in almost all patients during a medical abortion. The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 13 days after mifepristone intake, up to three weeks in some women). In a few cases, heavy bleeding may require surgical evacuation of the uterus. Bleeding is not in any way a proof of termination of pregnancy as it occurs also in most cases of failure.

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

- In 60%, expulsion occurs within 4 hours following misoprostol intake
- In the remaining 40% of the cases, expulsion occurs within 24 to 72 hours following misoprostol intake.

Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for 2 consecutive hours) may be a sign of incomplete abortion or other complications or an unnoticed extra-uterine pregnancy, and prompt medical or surgical intervention may be considered to prevent the development of hypovolemic shock. Patients should be counseled to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.

Women should expect to experience vaginal bleeding or spotting for an average of 9 - 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded / confirmed. She should be given precise instructions as to whom she should contact and where to go in the event of any problems, particularly in the case of very heavy vaginal bleeding.

In the event of an ongoing pregnancy diagnosed after the follow-up visit, termination by another method should be proposed to the woman.

Since heavy bleeding requiring haemostatic curettage occurs in 0 - 1.8% 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 specialized consultants according to the type of haemostatic disorder and the level of anaemia.

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

Excessive uterine / vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.

A follow-up visit must take place within a period of approximately 14 days after administration of mifepristone to verify by the appropriate means (clinical examination, ultrasound scan, and beta-hCG measurement) that expulsion / abortion has been completed and that vaginal bleeding has stopped or substantially reduced. In case of persistent bleeding (even light) beyond the control / follow-up visit, its disappearance should be checked within a few days. If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

### Infection and Sepsis

The genital tract is more susceptible to ascending infection when the cervix is dilated after abortion or childbirth. There are few data on the incidence of clinically significant pelvic infection after medical abortion, but it seems to be rare and probably occurs less often than after vacuum aspiration. Many of the symptoms of pelvic infection, such as pain, are often nonspecific and hence precise diagnosis is difficult. In particular, a sustained fever (> 4 hours) of 100.4°F or higher, severe pelvic / abdominal pain, pelvic / abdominal or adnexal tenderness in the days after a medical abortion may be an indication of infection and appropriate treatment should be given.

Very rare cases of fatal or serious toxic shock caused by pathogens like *Clostridium sordellii* endometritis, *Escherichia coli* presenting with or without fever or other obvious symptoms of

infection, have been reported after medical abortion with the use of 200mg mifepristone followed by non-authorized vaginal administration of misoprostol tablets for oral use. It cannot be excluded that this infection may occur also with vaginal misoprostol.

The Gynaecologist evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare, but potentially fatal complication.

A high index of suspicion is needed to rule out sepsis (e.g. *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhoea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leucocytosis with a marked left shift, tachycardia, haemoconcentration, and general malaise. Most of these deaths occurred in women who used vaginally administered misoprostol. No causal relationship between mifepristone, misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarean section), and in other gynaecologic and non-gynaecologic conditions.

### Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion. Medical abortion failures should be managed with surgical termination. Advise the patient whether you will provide such care or will refer her to another provider as part of counseling prior to prescribing mifepristone.

### Ectopic Pregnancy

Mifepristone is contraindicated in patients with a confirmed or suspected ectopic pregnancy since mifepristone is not effective for terminating these pregnancies. Gynaecologists 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 expected symptoms of a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed mifepristone.

Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

### Other risks

Pregnancy related symptoms such as nausea and vomiting may increase after mifepristone and increase further after misoprostol administration, and they will weaken and disappear during the abortion process. Lower abdominal pain and cramping are the most common symptoms and they are related to misoprostol administration and the abortion process. If pain persists after expulsion of the products of conception, its origin should be investigated. Diarrhoea is the most common dose related side effect related to misoprostol use which normally does not require treatment. Some women also report chills, shivering and/or temperature rise after misoprostol administration.

Any reproductive tract infections should be treated before the medical abortion regimen is administered.

### **Misoprostol**

The patient should not give misoprostol to anyone else.

- Misoprostol has been prescribed for the patient's specific condition, it may not be the correct treatment for another person, and may be dangerous to the other person if she is or were to become pregnant.
- Some authors suggest moistening misoprostol with 3 - 4 drops of saline / distilled water when used for vaginal administration.
- During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms. The patient should be given instructions on what to do if significant discomfort, excessive bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of misoprostol.

## **Drug Interactions**

### **Mifepristone**

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone). Whether this action has an impact on the efficacy of the dose regimen is unknown.

Based on *in vitro* inhibition information, co-administration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to 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.

### **Misoprostol**

Misoprostol has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Misoprostol does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin.

Misoprostol is predominantly metabolized via fatty acid oxidizing systems and has shown no adverse effect on the hepatic microsomal mixed function oxidase (P450) enzyme system. In specific studies, no clinically significant pharmacokinetic interaction has been demonstrated with antipyrine or diazepam. A modest increase in propranolol concentrations (mean approximately 20% in AUC, 30% in  $C_{max}$ ) has been observed with multiple dosing of misoprostol. In extensive clinical studies no drug interactions have been attributed to misoprostol. Drug interaction studies with misoprostol and several NSAIDs showed no clinically significant effect on the kinetics of ibuprofen, diclofenac, piroxicam, aspirin, naproxen or indomethacin. Concomitant administration of NSAIDs and misoprostol in rare cases can cause a transaminase increase and peripheral oedema.

Magnesium-containing antacids should be avoided during treatment with misoprostol as this may worsen the misoprostol-induced diarrhoea.

## **Use in Special Populations**

### ***Patients with Renal Impairment***

#### ***Mifepristone***

The effects of renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated. Mifepristone is not recommended in patients with renal impairment.

#### ***Misoprostol***

No routine dosage adjustment is recommended in patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

### ***Patients with Hepatic Impairment***

#### ***Mifepristone***

The effects of hepatic disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated. Mifepristone is not recommended in patients with hepatic impairment.

#### ***Misoprostol***

Misoprostol is metabolized by fatty acid oxidizing systems present in organs throughout the body. Its metabolism and plasma levels are therefore unlikely to be affected markedly in patients with hepatic impairment.

### ***Pregnant Women***

**MTP Kit** is indicated for use in the termination of pregnancy (through 63 days pregnancy) and has no other approved indication for use during pregnancy. In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen. There is currently no relevant clinical data that suggest the possible occurrence of malformation after the vaginal use of misoprostol during pregnancy. However, in a few cases where misoprostol was self-administered (orally or vaginally) in order to induce an abortion, the following deleterious effects of misoprostol have been suggested: malformations of limbs, of foetus movements and of cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements). To date, a risk of malformation cannot be excluded.

Consequently,

- Women should be informed that due to the non-negligible risk of failure of the medical method of pregnancy termination (which occurs in 4.5 to 7.8% of the cases) and to the unknown risk to the foetus, the post-treatment follow-up visit is mandatory;
- Should a failure of the method be diagnosed at the post-treatment visit (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data are too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultrasonographic monitoring of the pregnancy should be carried out in a specialised centre, with a special attention to the limbs.

### ***Teratogenic Effects***

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with mifepristone tablets, 200 mg in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with Mifepristone tablets, 200 mg in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Cases of ongoing pregnancies not terminated by surgical abortion at the end of treatment with mifepristone alone have reported of sirenomelia and cleft palate.

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the anti-progestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action. Animal studies have not evidenced teratogenicity of misoprostol but have shown its foetotoxicity at high doses.

### ***Non-teratogenic Effects***

The indication for use of **MTP Kit** is for the termination of pregnancy through 63 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

### ***Lactating Women***

#### ***Mifepristone***

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. However, no data is available. Consequently, mifepristone and misoprostol use should be avoided during breastfeeding. Since the effects of mifepristone on infants are unknown, breastfeeding women should consult with their Gynaecologist to decide if they should discard their breast milk for a few days following administration of the medications.

#### ***Misoprostol***

Misoprostol is rapidly metabolized in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. There are no published reports of adverse effects of misoprostol in breastfeeding infants of mothers taking misoprostol. Misoprostol should not be administered to nursing mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhoea in nursing infants.

The developmental and health benefits of breastfeeding should be considered along with any

potential adverse effects on the breastfed child from mifepristone in a regimen with misoprostol.

### **Paediatric Patients**

Safety and effectiveness of mifepristone and misoprostol in paediatric patients have not been established.

### **Effects on Ability to Drive and Use Machines**

No studies on the effects on the ability to drive and use machines have been performed.

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

### **Undesirable Effects**

#### **Mifepristone**

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive mifepristone and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day 3 of the treatment procedure. Women typically experience abdominal pain, including uterine cramping. Vaginal bleeding and uterine cramping are expected consequences of the action of mifepristone as used in the treatment procedure. Following administration of mifepristone and misoprostol, 80 to 90% of women reported bleeding more heavily than they do during a heavy menstrual period. Other commonly reported side effects were nausea, vomiting and diarrhoea. Pelvic pain, fainting, headache, dizziness and asthenia occurred rarely. Some adverse reactions reported during the 4 hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 - 35%. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively, so by day 14, reports were rare except for reports of bleeding and spotting.

#### ***Nervous System Disorders***

Rare: Headache, insomnia, anxiety, syncope.

#### ***Gastrointestinal Disorders***

Very common: Nausea, vomiting, diarrhoea (these gastrointestinal effects related to prostaglandin use are frequently reported), dyspepsia.

Common: Cramping, light or moderate.

#### ***Skin and Subcutaneous Tissue Disorders***

Uncommon: Hypersensitivity, skin rashes (0.2%).

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

Very rare: Angioedema

## ***Infections and Infestations***

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

Rare: Viral infection, vaginitis, sinusitis.

Very rare: Very rare cases of fatal toxic and septic shock (caused by *Clostridium sordellii* or *Escherichia coli*), presenting with or without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone followed by non-authorized vaginal administration of misoprostol tablets for oral use. The health care providers should be aware of this potentially fatal complication.

## ***Vascular Disorders***

Uncommon to Rare: Hypotension (0.25%)

## ***General Disorders and Administration Site Conditions***

Rare: Malaise, fatigue, vagal symptoms (hot flushes, dizziness), rigors (chills, shaking), fever, back pain, asthenia, leg pain, anaemia, fainting, decrease in hemoglobin greater than 2 g/dL.

## ***Reproductive System and Breast Disorders***

Very common: Uterine contractions or cramping (10 to up to 80%) in the hours following prostaglandin intake.

Common: Uterine haemorrhage, heavy bleeding occurs in about 5% of the cases and may require haemostatic curettage in up to 1.8% of the cases.

Rare: During induction of second trimester termination of pregnancy or labour induction for foetal death *in utero* during the third trimester, uterine rupture has been uncommonly reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar. Leucorrhoea and pelvic pain have also been reported.

## **Misoprostol**

### ***General***

- Gastrointestinal side effects like diarrhoea (usually dose related and self-limiting), abdominal pain, nausea, flatulence, dyspepsia, headache, vomiting and constipation
- Shivering
- Hyperthermia
- Dizziness

### ***Obstetrics and Gynaecological Use***

- Patient may experience pain due to uterine contractions
- Severe genital bleeding
- Shock
- Pelvic pain
- Uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy)

Women who received misoprostol during clinical trials reported the following gynaecological disorders: Spotting (0.7%), cramps (0.6%), hypermenorrhoea (0.5%), menstrual disorder (0.3%) and dysmenorrhoea (0.1%). Postmenopausal vaginal bleeding may be related to misoprostol administration. If it occurs, diagnostic workup should be undertaken to rule out gynaecological pathology.

### ***Incidence > 1%***

In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving misoprostol and may be causally related to the drug: Nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for misoprostol and placebo.

### ***Causal Relationship Unknown***

The following adverse events were infrequently reported. Causal relationships between misoprostol and these events have not been established but cannot be excluded:

Body as a Whole: Aches/pains, asthenia, fatigue, fever, rigors, weight changes.

Skin: Rash, dermatitis, alopecia, pallor, breast pain.

Special Senses: Abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.

Respiratory: Upper respiratory tract infection, bronchitis, bronchospasm, dyspnoea, pneumonia, epistaxis.

Cardiovascular: Chest pain, oedema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope, myocardial infarction (some fatal), thromboembolic events (e.g., pulmonary embolism, arterial thrombosis, and CVA).

Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.

Hypersensitivity: Anaphylactic reaction.

Metabolic: Glycosuria, gout, increased nitrogen, increased alkaline phosphatase.

Genitourinary: Polyuria, dysuria, haematuria, urinary tract infection.

Nervous system/Psychiatric: Anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.

Musculoskeletal: Arthralgia, myalgia, muscle cramps, stiffness, back pain.

Blood/Coagulation: Anaemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

Reproductive System and Breast Disorders: Vaginal haemorrhage (including postmenopausal bleeding), intermenstrual bleeding, menstrual disorder, uterine cramping, menorrhagia, dysmenorrhoea, uterine haemorrhage.

Congenital, Familial and Genetic Disorders: Birth defects.

### ***Post-marketing Experience***

The following adverse reactions have also been reported during post-approval use of mifepristone and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. No causal relationship between these events and mifepristone and misoprostol has been established:

Allergic reaction (including rash, hives, itching, anaphylaxis, angioedema), hypotension (including orthostatic), syncope, fainting, dyspepsia, back pain, leg pain, anaemia, lightheadedness, loss of consciousness, anxiety, pain, post-abortal infection (including endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis), uterine rupture, leukorrhoea, ruptured ectopic pregnancy, shortness of breath, and tachycardia (including racing pulse, heart palpitations, heart pounding), hematometra.

If you experience any side-effects, talk to your doctor or pharmacist or write to [drugsafety@cipra.com](mailto:drugsafety@cipra.com). You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PvPI on 1800 180 3024.

By reporting side-effects, you can help provide more information on the safety of this product.

## **Overdose**

### **Mifepristone**

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (nine-fold the recommended dose for termination of pregnancy). In the event of accidental massive ingestion, she should be observed closely as signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

### **Misoprostol**

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort being reported. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia. Symptoms should be treated with supportive therapy. It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage. In cases of overdose, standard supportive measures should be adopted as required.

## **Pharmacological Properties**

### **Mechanism of Action**

#### **Mifepristone**

Mifepristone (RU 486) is a synthetic steroid with an anti-progestational action as a result of competition with progesterone at the progesterone receptors.

#### **Misoprostol**

Misoprostol is a synthetic prostaglandin E<sub>1</sub>. At the recommended dosages, misoprostol induces

contractions of the smooth muscle in the myometrium and relaxation of the uterine cervix. The uterotonic properties of misoprostol should facilitate cervical opening and evacuation of the product of conception.

## **Pharmacodynamic Properties**

### **Mifepristone**

In women at doses of  $\geq 1$  mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy, it sensitizes the myometrium to the contraction-inducing action of prostaglandins. The maximum effect is achieved when prostaglandin was administered 36 to 48 hours after mifepristone.

During the first trimester, pre-treatment with mifepristone induces softening and dilatation of the cervix, that is detectable from 24 hours after administration of mifepristone and increases to a maximum at approximately 36 to 48 hours after administration. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data is available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95% of the cases and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results vary slightly. Combinations of mifepristone with prostaglandin analogues other than misoprostol and gemeprost have not been studied.

Mifepristone binds to the glucocorticoid receptor. In animals at doses of 10 to 25 mg/kg it inhibits the action of dexamethasone. In man the anti-glucocorticoid action is manifested at a dose  $\geq 4.5$  mg/kg by a compensatory elevation of adrenocorticotrophic hormone (ACTH) and cortisol. Glucocorticoid bioactivity may be depressed for several days following a single administration of 200 mg mifepristone for termination of pregnancy. The clinical implications of this are unclear; however, vomiting and nausea may be increased in susceptible women.

Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

### **Misoprostol**

When administered vaginally, the increase in uterine tonus begins after about 20 minutes and reaches its maximum after 46 minutes. Uterine contractility increases continuously for 4 hours after vaginal administration. Vaginal administration of misoprostol induces far more powerful and regular contractions than does oral administration.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to the expulsion of the conceptus. In clinical trials, the success rate is around 95% when 200 mg mifepristone is combined with misoprostol 800 mcg up to 63 days of amenorrhoea.

## **Pharmacokinetic Properties**

### **Mifepristone**

## ***Absorption***

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/L occurring approximately 90 minutes after ingestion. The absolute bioavailability of low doses of mifepristone (20 mg orally or intravenously) is 69%.

## ***Distribution***

Mifepristone is 98% bound to plasma proteins: albumin and alpha 1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, 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.

## ***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) RU 42 633, most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11beta; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

## ***Excretion***

By 11 days after a 600 mg dose of titrated compound, 83% of the drug has been accounted for by the faeces and 9% by the urine. Serum levels are undetectable by 11 days.

## ***Misoprostol***

Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid (misoprostol acid), which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogues.

In normal volunteers, misoprostol is rapidly absorbed after oral administration with a  $T_{\max}$  of misoprostol acid of  $12 \pm 3$  minutes and a terminal half-life of 20 - 40 minutes.

There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200-400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within 2 days.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid; however, this effect does not appear to be clinically important. After oral administration of radiolabeled misoprostol, about 80% of detected radioactivity appears in urine.

In contrast, after vaginal administration, the plasma concentration gradually increased, reaching maximum levels after 70 - 80 minutes and slowly declined with detectable levels present after 6 hours. Vaginal misoprostol was present in the circulation longer than oral misoprostol and hence its duration of stimulation of the uterus exceeds that of oral misoprostol. When misoprostol is

administered vaginally, the plasma concentrations of misoprostol acid peak in 1 - 2 hours and then decline slowly. Vaginal application of misoprostol results in slower increases and lower peak plasma concentrations of misoprostol acid than does oral administration, but overall exposure to the drug is increased.

## **Non-Clinical Properties**

### **Animal Toxicology or Pharmacology**

#### **Mifepristone**

Mifepristone is shown to have no mutagenic potential and no toxic effect up to 1000mg/kg in acute administration performed in mice and rats. In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogestosterone, anti-glucocorticoid and antiandrogenic) activity. In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose effect was observed. In monkeys, the number of fetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

#### **Misoprostol**

Single dose toxicity studies in rodents and nonrodents indicate a safety margin of at least 500 to 1000-fold between lethal doses in animals and therapeutic doses in humans. Reproductive toxicity studies in animals have shown embryotoxicity at high doses.

## **Description**

**MTP Kit** contains 1 tablet of mifepristone 200 mg to be given orally and 4 tablets of 200 mcg misoprostol to be given vaginally for the medical termination of pregnancy up to 63 days (9 weeks). This kit has been developed in accordance with guidelines issued by the Royal College of Obstetricians and Gynaecologists, UK.

## **Pharmaceutical Particulars**

### **Incompatibilities**

Not applicable

### **Shelf-life**

18 months

### **Packaging Information**

5 tablets in a blister pack

MTP Kit contains 1 tablet of mifepristone and 4 tablets of misoprostol.

## Storage and Handing Instructions

Store below 25°C.

## Patient Counselling Information

### 1. What is MTP Kit and what is it used for?

**MTP Kit** is a combination therapy containing two medicines called mifepristone and misoprostol. **MTP Kit** is indicated for the medical termination of intrauterine pregnancy of up to 63 days gestation based on the first day of your last menstrual period.

Mifepristone is an anti-hormone that acts by blocking the effects of progesterone, a hormone which is needed for pregnancy to continue. Misoprostol is a prostaglandin, which is a substance that increases contraction of the womb that will help expel the pregnancy. The two drugs can therefore, cause termination of pregnancy and must be used one after the other to give the best possible chance for the treatment to work.

### 1. What do you need to know before you take MTP Kit?

Do not take mifepristone and misoprostol tablets if -

- your pregnancy has not been confirmed by gynecological examination, ultrasound scan or biological tests,
- the first day of your last period was more than 63 days ago (if there is any doubt, the doctor can check the age of your pregnancy with a scanner),
- your doctor suspects an extra-uterine pregnancy (the egg is implanted outside the womb),
- you have bleeding disorders or are on blood-thinning drugs,
- you have undergone genital cutting or circumcision,
- you cannot return for a follow up visit to assess that the pregnancy is completely terminated,
- you cannot easily get emergency medical help in the 2 weeks after you take mifepristone and misoprostol,
- you are allergic to mifepristone, misoprostol (or any other prostaglandins) or any of the other ingredients of this medicine,
- you suffer from severe asthma which cannot be adequately treated with medication,
- you have hereditary porphyria (an inherited disorder of the blood),
- you suffer from chronic adrenal failure
- you have an intrauterine device (this must be removed prior to administering mifepristone tablet)

### **Warnings and Precautions**

In some circumstances the treatment may not be suitable for you, so please tell your doctor if:

- you have a heart complaint,
- your heart has been fitted with an artificial valve,
- you have a risk factors for heart diseases, such as high blood pressure or high blood cholesterol levels (increased fat content in your blood),
- you suffer from asthma,
- you suffer from an illness that may affect the clotting of your blood,
- you have liver or kidney disease,
- you are anaemic or otherwise malnourished.

The doctor will then be able to discuss with you if you are able to have the treatment.

### **Other Medicines and MTP Kit**

Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular, medicines containing the following active substances may interfere with the action of mifepristone and misoprostol:

- corticosteroids (used to treat asthma or inflammation),
- ketoconazole, itraconazole (used in antifungal treatment),
- erythromycin, rifampicin (antibiotics),
- St John's Wort (natural remedy used to treat mild depression),
- phenytoin, phenobarbital, carbamazepine (used to treat seizures or epilepsy).

The incidence of diarrhoea may be reduced by avoiding antacids that contain magnesium. If an antacid is needed, one that contains aluminium or calcium may be a more appropriate choice.

Ask your doctor about which medicines you can take for pain.

Talk to your doctor if you need to take any other medicines during the treatment.

### **MTP Kit with Food and Drink**

You should not drink grapefruit juice when you are treated with mifepristone and misoprostol.

### **Pregnancy and Breastfeeding**

Mifepristone and misoprostol may pass into breast milk and be taken in by your baby. You should stop breast feeding once you have taken the treatment. There is little information on the risks to the unborn baby. If the pregnancy continues and you decide to keep it, discuss this with your doctor who will arrange careful pre-natal monitoring and ultrasound examinations. It is recommended that you avoid becoming pregnant again before your next menstrual period after taking mifepristone and misoprostol.

### **Driving and Using Machines**

You should know that mifepristone and misoprostol may make you dizzy. Do not drive a car or operate machinery until you know how this medication affects you.

#### **1. How to Take MTP Kit**

- For pregnancies that have occurred with an intrauterine contraceptive device (coil) in place, this must be removed prior to administering mifepristone and misoprostol.
- It is recommended that you do not travel too far away from the prescribing hospital/clinic until the follow-up visit date. In an emergency or if you are worried for any reason, you can contact or return to the hospital/clinic before the appointment time. You will be given the telephone number to call for emergencies or any problems.

The use of mifepristone and misoprostol tablets requires your active participation as follows:

### **First Visit to the Hospital / Clinic**

- You will be given one tablet of mifepristone 200 mg to swallow with some water in the presence of a doctor.

- You will be able to go home after taking the tablet of mifepristone once the doctor is sure that you will not be sick. If you experience symptoms such as severe abdominal pain, fainting, fast heartbeat, fever lasting more than 4 hours after taking the tablet, please tell your doctor.
- In rare cases, the pregnancy may be expelled before you take the misoprostol tablets. It is essential that you return to the hospital/clinic to confirm that a complete pregnancy termination has occurred.

### **Follow-up Visit**

- You must return to the hospital/clinic 1-3 days after taking mifepristone, as directed by your doctor.
- You will be given 4 vaginal tablets of misoprostol to ensure the treatment is effective. The tablets will be placed into your vagina or you may do this yourself. In this case, please make sure that you empty your bladder and clean your hands thoroughly before inserting the misoprostol vaginal tablets. Push the four vaginal tablets one at a time up into the vagina as far as you can using your finger. It is recommended that you lie down for about 30 minutes after the misoprostol vaginal tablets have been inserted.
- You should stay in the hospital/clinic for a few hours or until you and the doctor are happy that you are well enough to go home. The pregnancy may be expelled within a few hours or during the next few days after misoprostol treatment.

### **Third Visit**

- You must return to the hospital/clinic for a check-up within approximately 14 days of taking the mifepristone tablet.
- It is important that you keep this appointment to check that your pregnancy has been completely expelled and you are well, as you will not be able to judge for yourself if the treatment has been successful.

### **After Treatment you Should be Aware that**

- Uterine bleeding usually starts 1 to 2 days after taking the mifepristone tablet. The bleeding lasts 2 or 3 weeks (on average 13 days). If the bleeding is heavy and prolonged, contact the doctor immediately for an earlier appointment.
- The presence of these bleedings is not related to the success of the method. If pregnancy continues or expulsion is incomplete, you will be offered a surgical method for terminating the pregnancy.
- If the pregnancy continues and you decide to keep it, discuss this with your doctor who will arrange careful pre-natal monitoring and ultrasound examinations.
- Important: It is possible for you to become pregnant again very soon after the pregnancy termination is complete. It is recommended that you avoid getting pregnant again soon after the termination. You should therefore start using a method of contraception within 3 to 9 days of taking the mifepristone tablet. Discuss contraceptive options with your doctor.

The use of mifepristone and misoprostol requires that measures are taken to prevent Rhesus factor sensitisation (*if you are Rhesus negative*) along with the general measures taken during any pregnancy termination.

### **If you Take More Mifepristone and Misoprostol than you Should**

As you will be supervised during administration of the treatment, it is unlikely that you will take more than you should.

## **If you Forget to take Mifepristone and Misoprostol**

If you forget to take any part of the treatment, it may not be fully effective. Talk with your doctor if you forgot to take the treatment.

*If you have any further questions on the use of this medicine, ask your doctor.*

### **1. Possible Side Effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

#### **Serious Side Effects**

Contact the hospital/clinic if you have:

- tearing of the womb after administration of prostaglandins in the second or third trimester of pregnancy, mainly in women with previous deliveries of a child or with a scar of a caesarean section.
- persistent heavy bleeding, for example soaking two sanitary pads per hour, for more than two hours
- persistent fever with a temperature of 38°C or higher, for more than four hours
- an unpleasant smelling discharge
- persistent pain unrelieved by medication.

*Contact your doctor if any of the following side effects gets serious or you are worried.*

#### **Very Common Side Effects (may affect more than 1 in 10 people)**

- uterine contractions or lower abdominal cramps in the hours following misoprostol.

#### **Common Side Effects (may affect up to 1 in 10 people)**

- heavy bleeding
- gastrointestinal cramping, light or moderate
- nausea, vomiting or diarrhoea.

#### **Uncommon Side Effects (may affect up to 1 in 100 people)**

- infection following abortion
- hypersensitivity: skin rashes.

#### **Rare Side Effects (may affect up to 1 in 1,000 people)**

- headaches
- malaise (feeling unwell)
- hot flushes, dizziness, chills
- fever
- low blood pressure
- hives and skin disorders, which can be serious.

#### **Very Rare Side Effects (may affect up to 1 in 10,000 people)**

- fatal toxic shock caused by infection by *Clostridium sordellii* endometritis, presenting without fever or other obvious symptoms of infection.

## **Reporting of Side Effects**

If you experience any side-effects, talk to your doctor or pharmacist or write to [drugsafety@cipla.com](mailto:drugsafety@cipla.com). You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PvPI on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

### **1. How to store MTP Kit**

Store below 25°C.

### **1. Contents of the pack and other information**

#### **What does MTP Kit contain**

**MTP Kit** contains 1 tablet of mifepristone 200 mg and 4 tablets of misoprostol 200 mcg each.

Mifepristone 200 mg tablet is a yellowish, uncoated, circular, biconvex that is plain on both sides.

Misoprostol 200 mcg tablets are white to off white, capsule shaped, biconvex, uncoated with central break-line on one side and plain on other side.

## **Details of Manufacturer**

Cipla Ltd.

Regd. Office Cipla House,

Peninsula Business Park, Ganpatrao Kadam Marg,

Lower Parel, Mumbai - 400 013

## **Details of Permission or Licence Number with Date**

Permission No: 789/ (52)/MFG/DFDA/2012/1815

Dated: 17.07.2012

Permission No: 789/ (52)/MFG/DFDA/2012/1817

Dated: 17.07.2012

## **Date of Revision**

26 November 2019