

MTPill

Mifepristone Tablets

COMPOSITION

Each uncoated tablet contains
Mifepristone 200 mg

DOSAGE FORM

Tablets for oral use.

DESCRIPTION

MTPill contains mifepristone, which has anti-progestational activity. As **MTPill** inhibits the activity of progesterone it results in termination of pregnancy. **MTPill** also exhibits antigluccorticoid and weak anti-androgenic activity.

PHARMACOLOGY

Pharmacodynamics

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins. Mifepristone also exhibits antigluccorticoid and weak antiandrogenic activity. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotrophic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

Pharmacokinetics

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 a 20 mg oral dose 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 11 β ; 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.

INDICATIONS

MTPill is indicated for the medical termination of intrauterine pregnancy through **49 days** pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual

period in a presumed **28 days** 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 **MTPiII** begins. Patients taking **MTPiII** must take 400 mcg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when **MTPiII** and misoprostol fail to cause termination of intrauterine pregnancy.

DOSAGE AND ADMINISTRATION

Treatment with Mifepristone (**MTPiII**) requires concurrent administration of misoprostol. Treatment with **MTPiII** and misoprostol for the termination of pregnancy requires three doctor visits by the patient. **MTPiII** may be administered only in a clinic, medical office, or hospital, 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.

Day One : MTPiII Administration

Three 200 mg tablets (600 mg) of **MTPiII** are taken in a single oral dose.

Day Three : Misoprostol Administration

The patient returns to the healthcare provider two days after ingesting **MTPiII** . Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200-mcg tablets (400 mcg) of misoprostol orally.

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 the misoprostol.

Day 14: Post-Treatment Examination

Patients will return for a follow-up visit approximately **14 days** after the administration of **MTPiII**. 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 MTPiII and misoprostol for the termination of pregnancy (the “treatment procedure”) is contraindicated in patients with any one of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy)
- IUD in place
- Chronic adrenal failure
- History of allergy to mifepristone, misoprostol or other prostaglandin
- Haemorrhagic disorders or concurrent anticoagulant therapy
- Inherited porphyria

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 physician.

WARNINGS AND PRECAUTIONS

Bleeding: Vaginal bleeding occurs in almost all patients during the treatment procedure. In general the duration of bleeding and spotting increased as the duration of the pregnancy increased. Normally it lasts for an average of **9 to 16 days**.

In some cases, excessive bleeding may require treatment by vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.

Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and require prompt and immediate medical attention.

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. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

Infections and Sepsis

Cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported. No causal relationship between these events and use of **MTPill** and misoprostol has been established. A sustained fever of 100.4 degree or higher, severe abdominal pain, or pelvic tenderness in the days after medical abortion may indicate infection. Atypical presentation of serious infection and sepsis without these symptoms but with significant leucocytosis, tachycardia or haemoconcentration can occur.

Ectopic pregnancy

MTPill is contraindicated in confirmed or suspected ectopic pregnancy since it is not effective for terminating these pregnancies. There could be a 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 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 **MTPill**.

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 **MTPill** may be lower if misoprostol is administered more than two days after mifepristone administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted in vitro and in animals have revealed no genotoxic potential for mifepristone.

Drug Interactions

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, 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 include mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 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 CYP 3A4

substrates and have narrow therapeutic range, including some agents used during general anaesthesia.

Pregnancy

Mifepristone is indicated for the use in the termination of pregnancy (through **49 days** pregnancy) and has no other approved indication for use during pregnancy.

Teratogenic Effects

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.

Nonteratogenic Effects

The indication for use of **MTPill** in conjunction with misoprostol is for the termination of pregnancy through **49 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.

Lactation

It is not known whether **MTPill** is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their doctor to decide if they should discard their breast milk for a few days following administration of the medications.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

MTPill is available only in single dose packaging. Administration must be under the supervision of a gynaecologist (see Dosage and Administration).

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 **MTPill**. 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, hematocrit and red blood cell count occur in some women who bleed heavily.

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.

UNDESIRABLE EFFECTS

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 **MTPill** 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 three of the treatment procedure. Women typically experience abdominal pain, including uterine cramping. 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 four 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 to 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.

Serious bacterial infection, bleeding, ectopic pregnancies that have ruptured, and death, including another death from sepsis were recently reported.

OVERDOSAGE

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 threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg (about 10 times the human dose recommended for termination of pregnancy).

STORAGE AND HANDLING INSTRUCTIONS

Store below 30°C.

PACKAGING INFORMATION

MTPill tablets is a pack of 3 strips containing 1 tablet each.

PATIENT INFORMATION

Read this information carefully before taking **MTPill** (along with misoprostol) . It will help you understand how the treatment works. This Medication Guide is not a substitute for your doctor's advice.

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

- The necessity of completing the treatment schedule, including a follow-up visit approximately **14 days** after taking **MTPill** ;
- That vaginal bleeding and uterine cramping probably will occur;
- That prolonged or heavy vaginal bleeding is not proof of a complete expulsion;
- That if the treatment fails, there is a risk of foetal malformation;
- That medical abortion treatment failures are managed by surgical termination; and
- 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

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

What is **MTPill**?

MTPill blocks a hormone needed for your pregnancy to continue. When used together with another medicine called misoprostol, **MTPill** can end your pregnancy of **49 days**.

How should I take **MTPill**?

• **Day 1**

- Your doctor will discuss the benefit and risk of using **MTPill**.
- After getting a physical examination, if advised by your Doctor, take 3 tablets of **MTPill** .

• **Day 3**

- Your Doctor will check to see if you are still pregnant.
- If you are still pregnant, your doctor will advise you to take 2 misoprostol tablets.
- If you get cramps, nausea, diarrhoea, and other symptoms, inform your Doctor. Your
- Doctor may send you home with medicines for these symptoms.

On Day 14

- This follow-up visit is very important. You must return to the Doctor about 2 weeks after you took **MTPill** to be sure you are well and that you are not pregnant.

- Your Doctor will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your Doctor will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

Who should not take MTPill?

Some women should not take **MTPill** .

Do not take it if:

- It has been more than **49 days** (7 weeks) since your last menstrual period began
- You have an IUD (a contraceptive device put in the uterus). It must be taken out before you take **MTPill**
- Your doctor has told you that you have a pregnancy outside the uterus (ectopic pregnancy)
- You have problems with your adrenal glands (chronic adrenal failure)
- You take a medicine to thin your blood
- You have a bleeding problem
- You take certain steroid medicines
- You cannot return for the next 2 visits
- You cannot easily get emergency medical help in the 2 weeks after you take **MTPill**
- You are allergic to MTPill or misoprostol. Tell your Doctor about all your medical conditions to find out if you can take **MTPill** . Also, tell your Doctor if you smoke at least 10 cigarettes a day.

What should I avoid while taking MTPill and misoprostol ?

You should not take certain other medicines, because they may interfere with the treatment. Ask your Doctor about what medicines you can take for pain. Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your doctor about them.

If you are breast-feeding at the time you are advised to take **MTPill** and misoprostol , discuss with your doctor if you should stop breast-feeding for a few days.

What are the possible side effects of using MTPill?

Symptoms to expect -

This treatment causes cramping and bleeding. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramps and bleeding and still be pregnant. This is why you must return to your doctor on **Day 3** and on **Day 14**.

If you are not already bleeding after taking **MTPill** , you probably will begin to bleed once you take misoprostol. This is the medicine you take on **Day 3**. This is an expected part of ending the pregnancy. Bleeding or spotting can be expected for an average of **9-16 days** and may last for up to **30 days**. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue that come from your uterus.

Heavy bleeding and the need for surgery -

In some cases, bleeding can be very heavy. In a very few cases, this bleeding will need to be stopped by a surgical procedure. Contact your Doctor right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding.

What has to be done if you are still pregnant after MTPill and misoprostol treatment?

If you are still pregnant, your Doctor will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using a birth control method as soon as your pregnancy ends or before you start having sexual intercourse again.