

Data Sheet

MIFEGYNE

Mifepristone micronised 200 mg tablets

Active substance	Mifepristone micronised	200 mg
Excipients or other ingredients (all of mineral or vegetable origin)	Anhydrous colloidal silica	3 mg
	Maize starch	102 mg
	Povidone	12 mg
	Microcrystalline cellulose	30 mg
	Magnesium stearate	3 mg

Presentation

Light yellow, cylindrical, bi-convex tablets, for oral administration. Blister pack (PVC and aluminium foil and carton) containing 3 tablets of Mifegyne 200 mg. Medicines classification: Prescription medicine.

Uses

Actions:

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors. In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. In pregnancy it sensitises the myometrium to the contraction-inducing action of prostaglandin. It is an abortifacient. It does not bind to mineralocorticoid receptors; therefore the risk of acute adrenal failure during mifepristone intake is negligible. It binds to the glucocorticoid receptors. In animals at doses of 10-25 mg/kg it inhibits the action of dexamethasone. 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.

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

Pharmacokinetics:

After oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed. The peak concentration of 1.98 mg/ml is reached after 1.3 hrs (mean of 10 subjects). There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hrs and then more rapidly, giving an elimination half-life of 18 hrs. With radio receptor assay techniques, the terminal half-life is up to 90 hrs, including all metabolites of mifepristone able to bind to progesterone receptors. After administration of low doses of mifepristone (20 mg orally or intravenously) the absolute bioavailability is 69%. In plasma, mifepristone is 98% bound to plasma proteins: albumen and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG. N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism. After administration of a 600 mg labelled dose of mifepristone, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces. Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk.

Indications:

1. As a medical alternative to surgical termination of intra-uterine pregnancy
 2. Softening and dilatation of the cervix uteri prior to surgical pregnancy termination
 3. Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons
 4. Labour induction for the expulsion of a dead fetus (fetal death in utero).
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Dosage and Administration

There are no precautions for timing in relation to food.

1. As a medical alternative to surgical termination of intra-uterine pregnancy in early pregnancy: 600 mg mifepristone (3 tablets) in a single oral dose followed 36-48 hrs later, by the administration of a prostaglandin analogue; misoprostol 400 mcg orally (up to 49 days) or gemeprost 1 mg vaginally (up to 63 days).
2. Softening and dilatation of the cervix uteri prior to surgical pregnancy termination: 200 mg mifepristone (one tablet), followed 36-48 hrs later (but not beyond) by a surgical termination of pregnancy.
3. Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons (to reduce the doses of prostaglandin): 600 mg of mifepristone (3 tablets) taken in a single oral dose, 36-48 hrs prior to scheduled prostaglandin administration which will be repeated as often as indicated.
4. Labour induction for expulsion of a dead fetus (fetal death in utero): 600 mg of mifepristone in a single oral daily dose for 2 consecutive days. Mifegyne alone leads

to expulsion in about 60%. Labour should be induced by the usual methods if it has not started within 72 hrs following the first administration of mifepristone.

Contraindications

Mifegyne must not be administered if there is doubt as to the existence or age of the pregnancy or if an extra-uterine pregnancy is suspected. An ultrasound scan and/or measurement of Beta-hCG must be performed before administration. For first trimester abortions, Mifegyne is contraindicated if the pregnancy is beyond 49 days of amenorrhoea when used with misoprostol, or beyond 63 days of amenorrhoea when used with gemeprost.

Mifegyne should never be prescribed in the following situations: chronic adrenal failure, known allergy to mifepristone or to any component of the product, severe asthma uncontrolled by corticosteroid therapy, porphyrias. It must not be used if there are contraindications to the prostaglandins used in conjunction with Mifegyne.

As a precaution and in the absence of specific studies, Mifegyne should not be used in patients with renal failure, liver failure or malnutrition, or during breast feeding. Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk, however no data is available.

Warnings and Precautions

General measures usually taken during pregnancy termination must be observed, including determination of blood group and rhesus factor. Mifegyne is unlikely to have an effect on the ability to drive or use machines. During initial clinical trials, rare serious **cardiovascular accidents** have been reported following the intra-muscular administration of a prostaglandin analogue. For this reason women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

In case of suspected **acute adrenal failure**, dexamethasone administration is recommended - 1mg of dexamethasone antagonises a dose of 400mg of mifepristone. Due to the antiglucocorticoid activity of mifepristone, the efficacy of **long-term corticosteroid** therapy may be decreased during the 3-4 days following Mifegyne intake. Therapy should be adjusted. In patients with **asthma** using inhaled corticosteroid therapy, it is recommended that the dose be doubled during the 48 hrs preceding administration of mifepristone and continue for about one week.

In patients with insulin dependent **diabetes**, the occurrence of gastro-intestinal disorders induced by the pregnancy or by the treatment, may alter insulin requirements.

Contraception: During clinical trials, pregnancies occurred between fetal expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle using reliable contraception. Where a pregnancy occurs with an intra-uterine device in situ, the device must be removed before administration of mifepristone.

Teratogenicity: No effect was observed in rats and mice surviving fetal exposure. In rabbits however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of fetal 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. Uncommon cases of malformations have occurred in the human fetus or infant but the exact role of mifepristone, prostaglandin analogue or coincidental event is unknown. Patients must be informed that in the event of failure and a continuing pregnancy the fetus may be exposed to a risk of malformation. Should the patient wish to continue with her pregnancy, the available data is too limited to justify essential termination of an exposed pregnancy. In that event careful ultrasonographic monitoring of the pregnancy is recommended.

Failures: In clinical trials, the results vary according to the prostaglandin used and the time of administration. The success rate is up to 95.7% when misoprostol is used orally up to 49 days of amenorrhoea, and with gemeprost applied vaginally it reaches 98.7% up to 49 days of amenorrhoea and 94.8% up to 63 days of amenorrhoea. Failures occur in 1.3 to 7.5%, of which 0-1.5% are ongoing pregnancies, 1.3-4.6% are due to incomplete expulsion and 1.4% require haemostatic curettage.

Bleeding: Heavy bleeding requiring curettage occurs in 0 to 1.4% of patients. Special care should be given to patients with haemorrhagic disorders, hypocoagulability or anaemia. The decision to use a medical or surgical method should be decided with relevant specialist consultation.

In the case of first trimester abortion the patient must be informed of the occurrence of prolonged vaginal bleeding (lasting an average of about 12 days after Mifegyne intake) which may be heavy. Bleeding occurs in almost all cases and is not proof of complete expulsion. The patient should be informed that expulsion may take place before prostaglandin administration in about 3% of cases. This does not preclude the follow-up visit to check for complete expulsion. The patient should be informed not to travel far away from the prescribing centre until complete expulsion has been confirmed. She must receive precise instructions about who to contact and where to go, in the event of problems, particularly in the case of very heavy vaginal bleeding. A follow up visit must take place within a period of 14 to 21 days after administration of Mifegyne to verify by the appropriate means (such as clinical examination, ultrasound scan or beta-hCG measurement) that expulsion is complete and that vaginal bleeding has stopped. Persistent bleeding (even light) at this point could indicate incomplete abortion, or an unnoticed extra-uterine pregnancy and appropriate treatment should be considered. If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate viability.

In the case of softening and dilatation of the cervix prior to surgical termination the woman must be informed of the risk of bleeding and of the rare occurrence (0.9%) of expulsion prior to surgical termination.

Infection and sepsis: Although infection following medical abortion is rare clinicians must be alert to the possibility of pelvic infection in the days after a medical abortion especially if there is a sustained fever or severe abdominal pain or pelvic tenderness.

Very rare cases of fatal toxic shock caused by *Clostridium sordellii* endometritis have been reported in North America but not in Europe. These cases have presented atypically without obvious symptoms such as fever, pain or tenderness but with signs including significant leucocytosis, tachycardia or haemoconcentration. These cases occurred after medical abortion with the use of 200mg mifepristone followed by non-authorized vaginal administration of misoprostol tablets. Clinicians should be aware of this potentially fatal complication.

Adverse Effects

Urogenital: It is very common for women to experience uterine contractions or cramping (10-45%) in the hours following prostaglandin intake. Bleeding increases with gestational age. Heavy bleeding occurs in about 5% of cases and from 0-1.4% may require haemostatic curettage. Uterine rupture has been uncommonly reported after prostaglandin intake for induction of second trimester termination or labour induction for fetal death, particularly in multiparous women or those with a caesarian scar.

Gastrointestinal: Nausea, vomiting and diarrhoea are very common after prostaglandin intake. Light to moderate cramping is common.

Cardiovascular: Rarely, hypotension (0.25%)

Hypersensitivity and skin: Uncommonly, skin rashes (0.2%). Single cases of urticaria, erythroderma, erythema nodosum and epidermal necrolysis have been reported.

Other systems: Vagal symptoms are common (hot flushes, dizziness, chills). Fever is uncommon. Rare cases of headaches, malaise have been reported.

Interactions

No interaction studies have been performed. 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, rifampicin, dexamethasone, St John's Wort and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on invitro 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 interactions 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.

A decrease of the efficacy of the prostaglandin can theoretically occur due to the anti-prostaglandin properties of non-steroidal anti-inflammatory drugs including aspirin.

Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

Overdosage

Single doses of mifepristone up to 2G caused no unwanted reaction. In the event of massive ingestion, signs of adrenal failure might occur. Acute intoxication may require admission to hospital and if relevant treatment with dexamethasone.

Pharmaceutical Precautions

No known incompatibilities. Shelf life 3 yrs.

Medicine Classification

Prescription medicine.

Further Information

Mifegyne must only be used in accordance with the legislation governing termination of pregnancy. It must be prescribed by a doctor and administered by a health professional in a licensed premise. It will not be available through pharmacies.

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