

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mifepristone 200mg tablets ¹

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg mifepristone.

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Tablet.

Yellowish, round biconvex tablets, debossed with M1 on one side. The other side is plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mifepristone 200mg tablets is indicated for:

1) Medical termination of developing intra-uterine pregnancy.

In sequential use with a prostaglandin analogue, up to 84 days of amenorrhea (see section 4.2).

2) Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.

3) Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons (*beyond the first trimester*).

Mifepristone 200mg tablets should be prescribed and administered in accordance with countries' national laws and regulations.

The most recent official guidelines should be taken into consideration for deciding on the appropriateness of therapy with mifepristone .

Official guidance will normally include WHO and public health authorities guidelines (see sections 4.4 and 5.1, and weblinks in reference section at end of this document).

4.2 Posology and method of administration

1) Medical termination of developing intra-uterine pregnancy

The method of administration will be as follows:

Up to 49 days of amenorrhea:

200 mg of mifepristone (i.e. 1 tablet of 200 mg) is taken in a single oral dose, followed 24 to 48 hours later by the administration of 400 µg of the prostaglandin analogue misoprostol orally, or 800 µg misoprostol per vaginal, buccal or sublingual route.

Between 50-63 days of amenorrhea

200 mg of mifepristone (i.e. 1 tablet of 200 mg) is taken in a single oral dose, followed 24 to 48 hours

¹ Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

later by the administration of 800 µg misoprostol per vaginal, buccal or sublingual route.

Between 64 and 84 days

200 mg mifepristone (i.e. 1 tablet of 200 mg) is taken in a single oral dose, followed 36 to 48 hours later by 800 µg misoprostol administered vaginally in a health-care facility. Subsequent misoprostol doses should be 400 µg, administered either vaginally or sublingually, every 3 hours up to four further doses until expulsion of the product of conception.

2) Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester

200 mg of mifepristone (one tablet), followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

3) Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons (*beyond the first trimester*)

200 mg of mifepristone (i.e. 1 tablet of 200 mg) is taken in a single oral dose, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated:

400 µg oral or 800 µg vaginal misoprostol followed by 400 µg vaginal or sublingual misoprostol every 3 hours up to a maximum of five doses, administered in a health-care facility. For pregnancies of gestational age greater than 24 weeks, the dose of misoprostol should be reduced due to the greater sensitivity of the uterus to prostaglandins. The lack of clinical studies precludes specific dosing recommendations.

Gemeprost is a prostaglandin analogue similar to misoprostol. However, according to current guidelines, e.g. those by WHO, misoprostol is recommended as the prostaglandin analogue of choice for the induction of abortion

Special populations

Paediatric population

Only limited data are available on the use of mifepristone in adolescents.

Hepatic and renal failure

Mifepristone 200mg tablets is not recommended in patients with severe hepatic or renal disease (see section 4.4) due to the lack of data.

4.3 Contraindications

This product SHOULD NEVER be prescribed in the following situations.

IN ALL INDICATIONS

- Chronic adrenal failure
- Hypersensitivity to the active substance or to any of the excipients
- Severe asthma uncontrolled by therapy
- Inherited porphyria.

In the indication: medical termination of developing pregnancy

- Pregnancy not confirmed by gynaecological examination, ultrasound scan or biological tests
- Pregnancy beyond 84 days of amenorrhoea,
- Suspected extra-uterine pregnancy
- Contra-indication to the prostaglandin analogue selected.

In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy

- Pregnancy not confirmed by ultrasound scan or biological test
- Pregnancy of 84 days of amenorrhea and beyond
- Suspected extra-uterine pregnancy.

In the indication: Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons (*beyond the first trimester*):

- Contraindications to the prostaglandin analogue selected

4.4 Special warnings and special precautions for use

Warnings

Mifepristone 200mg tablets should never be used in women with ongoing pregnancy who want to complete it. The age of the pregnancy must be determined from the questioning and the clinical examination of the patient. Uterine ultrasound is recommended.

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

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

1) Medical termination of developing intra-uterine pregnancy

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

- The necessity to combine treatment with prostaglandin to be administered 24-48 hours after administration of this medicine,
- The possible failure of the method, requiring pregnancy termination by another method.

A follow-up visit within 7 to 14 days after intake of mifepristone 200 mg tablets may be required depending on the individual situation.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of mifepristone 200 mg tablets.

The expulsion may take place before prostaglandin administration (in about 3% of cases).

Before mifepristone is given to a woman who has undergone genital mutilation (FGM) a physical examination must be performed by a qualified trained medical professional to exclude any anatomical obstacles to medical abortion.

Risk related to the method

- Failures

Failure occurs in 1.3 to 7.5% of the cases.

In the rare case of non-complete expulsion, a surgical revision may be necessary.

The efficacy of the method decreases with parity, and consequently increasing age of the woman.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 9 days or more after mifepristone 200 mg tablets intake) which may be heavy. Bleeding occurs in almost all cases and is not a proof of complete expulsion.

Before leaving the facility women should receive oral and written instructions about how to care for themselves after they leave. These instructions should include: how much bleeding to expect, how to recognize potential complications, and how and where to seek help if required.

- Follow-up visit

Following uncomplicated surgical and medical abortion using mifepristone with misoprostol, routine follow-up visits are not necessary. For women who wish to return to the clinic, a follow-up visit may be scheduled at 7–14 days after the procedure. Women should be advised that additional services are available to them if needed or desired, e.g. if they experience signs of ongoing pregnancy.

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

Heavy bleeding requiring haemostatic curettage has been reported to occur in 0 to 1.4% of the cases during medical abortion, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia.

- Infection

Serious cases (including fatal cases) of toxic shock and septic 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 mifepristone tablets followed by misoprostol tablets. Clinicians should be aware of this potentially fatal complication.

- Other risks

Pregnancy-related symptoms such as nausea and vomiting may increase after mifepristone, and they will weaken and disappear during the abortion process.

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

2) Softening and dilatation of the cervix uteri prior to surgical pregnancy termination

For the full efficacy of therapy, the use of Mifepristone 200mg tablets must be followed, 36 to 48 hours later and not beyond, by surgical termination.

Risks related to the method

- Bleeding

Before leaving the facility women should receive oral and written instructions about how to care for themselves after they leave. These instructions should include: how much bleeding to expect, how to recognize potential complications, and how and where to seek help if required. Heavy bleeding requiring curettage occurs in about 1% of patients. Special care should be given to patients with haemostatic disorders, hypocoagulability, or severe anaemia.

- Other risks

They are those of the surgical procedure.

Precautions for use

In all instances

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

Due to the antiglucocorticoid 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.

Rhesus allo-immunisation

Tests for Rhesus (Rh) blood group typing should be provided when feasible, to administer Rh-immunoglobulin for the prevention of rhesus allo-immunisation, when indicated.

Contraception initiation after medical termination of pregnancy

During clinical trials, pregnancies occurred between embryo 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. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

Medical termination of developing intra-uterine pregnancy

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

The precautions related to the prostaglandin analogue used should be followed where relevant.

4.5 Interaction with other medicinal products and other forms of interaction

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 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, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine, including some agents used during general anaesthesia.

Combination with non-steroidal anti-inflammatory drugs

Theoretically, concomitant use with non-steroidal anti-inflammatory drugs may reduce the efficacy of the method. However, no clinically meaningful effect has been shown upon co-administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animals, the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule (see section 5.3).

With subabortive doses, isolated cases of malformations are observed in rabbits, but not in rats or mice, and are too few to be considered significant, or attributable to mifepristone.

In clinical practice, rare cases of malformations of the extremity of lower limbs (out of them, club-foot) have been reported in case of mifepristone administered alone or associated with prostaglandins. One of the possible mechanisms might be amniotic band syndrome. However, data is too limited to determine whether the molecule is a human teratogen.

Consequently,

- Should a failure of the method be diagnosed (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 is too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultrasound monitoring of the pregnancy will be established, with a special attention to the limbs.

Lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breastfeeding.

Fertility

Mifepristone 200mg tablets does not affect fertility. It is possible that the women becomes pregnant again as soon as the termination of the pregnancy is completed. Therefore, it is important to inform the patient to start contraception immediately after the termination of the pregnancy.

4.7 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 200mg tablets may cause dizziness, which could have an effect on the ability to drive and use machines.

4.8 Undesirable effects

The most frequently (>1/10) reported adverse reactions of the regimens are nausea, vomiting, diarrhoea and uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.

The following adverse reactions have been observed and reported during treatment with {product name} with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Organ Class	Very common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Infection following abortion (<5%) Endometritis Pelvic inflammatory disease			Fatal toxic shock syndrome (see section 4.4)
Nervous system disorders				Headache	
Vascular disorders			Hypotension (0.25%)		
Gastrointestinal disorders	Nausea Vomiting Diarrhoea	Cramping, light or moderate			
Skin and subcutaneous tissue disorders			Hypersensitivity Skin rashes (0.2%)	Urticaria Erythroderma Erythema nodosum, Toxic Epidermal Necrolysis	Angioedema

System Organ Class	Very common	Common	Uncommon	Rare	Very Rare
Reproductive system and breast disorders	Uterine contractions and cramping (10-45%) in the hours following prostaglandin intake	Heavy bleeding*		Uterine rupture **	
General disorders and administration site conditions				Malaise Vagal symptoms (hot flushes, dizziness, chills) Fever	

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

**During induction of second trimester termination of pregnancy uterine rupture has been reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.

4.9 Overdose

No case of overdose has been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other sex hormone and modulator of the reproductive function/antiprogestogen.

ATC code: G03XB01

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

At doses ranging from 3 to 10 mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey).

In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandin. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. 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.

For 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 percent 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.

Mifepristone with misoprostol has been proven highly effective, safe and acceptable for abortion up to 9 weeks since last menstrual period. Efficacy rates up to 98% are reported. Approximately 2-5% of women treated with the combination of mifepristone and misoprostol will require surgical intervention to resolve an incomplete abortion, terminate a continuing pregnancy or control bleeding.

In an uncontrolled study with mifepristone with misoprostol in women at a gestational age 63 to 90 days successful termination of pregnancy was observed in 91.7%

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 200 mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

Gemeprost is a prostaglandin analogue similar to misoprostol, but it is more expensive, requires refrigeration, and may only be administered vaginally. Thus, although gemeprost demonstrates similar efficacy as misoprostol, misoprostol is the prostaglandin analogue of choice for abortion-related care. 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 antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol. Glucocorticoid bioactivity (GBA) 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.

5.2 Pharmacokinetic properties

Absorption

After oral administration of a single dose of 200 mg mifepristone is rapidly absorbed.

Following administration of mifepristone 200 mg Tablets as single dose in healthy volunteers, mean (SD) mifepristone C_{max} was 2.3 µg/ml (0.85 µg/ml) and the mean (SD) AUC_{0-72h} was 42.3 µg•hour/ml (17.5 µg•hour/ml). The reported mean t_{max} is about 1.5 hours.

Distribution

In plasma mifepristone is 98% bound to plasma proteins: albumin 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.

Metabolism

Mifepristone is extensively metabolized in the liver by CYP3A4. N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Elimination

Mifepristone is excreted in feces (83%) and in urine (9%) with an initial elimination half-life of 12-72 hours and a terminal elimination half-life of 18 hours.

5.3 Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogestone, antiglucocorticoid 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 effect was dose-dependent. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment. No evidence of teratogenicity was observed in post-implantation rat and monkey embryos exposed to mifepristone in vitro.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, corn starch, povidone, magnesium stearate, microcrystalline cellulose.

Incompatibilities

Not applicable.

6.2 Shelf life

36 months

6.3 Special precautions for storage

Do not store above 30°C.

Protect from light. Store in the original package.

6.4 Nature and contents of container

1 Tablet (single dose) or 3 Tablets (hospital pack) are packaged in a PVC/aluminium blister and are supplied in individual cartons.

6.5 Instructions for use and handling and disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

RH 052

9. DATE OF FIRST PREQUALIFICATION

15 August 2016

10. DATE OF REVISION OF THE TEXT

March 2017. Section 2 and 6 updated in June 2018.

Detailed information on this medicinal product is available on the website of the WHO Prequalification Programme <https://extranet.who.int/prequal/>.

Reference list

General reference:

This text is primarily based on:

Safe abortion: technical and policy guidance for health systems. Second edition, WHO Geneva, 2012 at http://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241548434/en/

1. EXELGYN, SmPC of Mifegyne®, approved by the Medicines Evaluation Board in the Netherlands on 25 August 1999 and revised on 15 April 2014.

2. Sun Pharmaceutical Industries Europe B/V., SmPC of Medabon®, approved by the MHRA in the UK on 17 May 2012 and revised on 12 June 2012.

Section 5.1:

Løkeland M1, Iversen OE, Dahle GS et al: Medical abortion at 63 to 90 days of gestation. *Obstet Gynecol.* 2010 May;115(5):962-8. doi: 10.1097/AGG.0b013e3181da0c3e.

Section 5.2:

Mifepristone: Indications, Side Effects, Warnings - Drugs.com:

<https://www.drugs.com/monograph/mifepristone.html>

(last accessed on 2017-02-06)