WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH052 trade name]†

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 tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'M1' debossed (stamped into) one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH052 trade name] is indicated, in sequential use with a prostaglandin analogue (misoprostol) for:

- **Induction of abortion**
- **Missed abortion**
- **Intrauterine fetal death**

[RH052 trade name] is also indicated for **cervical priming prior to surgical termination of pregnancy during the first trimester**.

Decisions on the appropriate use of [RH052 trade name] should take into account the most recent WHO treatment guidelines, supplemented by other authoritative guidelines. It should be prescribed and given in accordance with countries' national laws and regulations.

4.2 Posology and method of administration

Posology

Induction of abortion

When used for induction of medical abortion (termination of pregnancy) in line with relevant guidelines and national regulations, the following regimens should be used, depending on gestational age.

At less than 12 weeks:

Treatment should begin with a single tablet of mifepristone 200 mg *orally*, followed after 24 to 48 hours by misoprostol 800 µg (4 × 200-µg tablets) by the *vaginal*, *sublingual* or *buccal* route.

Further doses of misoprostol may be needed to achieve successful abortion.

At 12 weeks or more:

Treatment should begin with a single dose of mifepristone 200 mg *orally*, followed after 24 to 48 hours by misoprostol 400 µg (2 × 200-µg tablets) by the *vaginal*, *sublingual* or *buccal* route every 3 hours as needed, until abortion is successful.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Missed abortion

Where medical management is considered appropriate for missed abortion at gestational ages less than 14 weeks, patients should receive a single tablet of mifepristone 200 mg *orally*, followed after at least 24 hours by misoprostol 800 µg (4 × 200-µg tablets) by the *vaginal, sublingual* or *buccal* route.

Intrauterine fetal death

For medical management of intrauterine fetal death between 14 and 28 weeks' gestational age, treatment should begin with a single dose of mifepristone 200 mg *orally*, followed after 24 to 48 hours by misoprostol 400 µg (2 × 200-µg tablets) by the *sublingual* or *vaginal* route every 4 to 6 hours as needed, until abortion is successful.

Cervical priming

Where cervical priming is considered appropriate before surgical abortion, [RH052 trade name] may be given in a single dose of 200 mg by mouth 24 to 48 hours before the surgical procedure. For priming before surgical abortion at gestational ages of 12 weeks or more, it may be combined with misoprostol, an osmotic dilator, or both.

Renal impairment

Mifepristone is not recommended in patients with severe renal impairment due to lack of data.

Hepatic impairment

In the absence of relevant studies, [RH052 trade name] is not recommended in women with hepatic failure.

Method of administration

[RH052 trade name] is taken *orally*. It should be swallowed whole and not broken or crushed.

4.3 Contraindications

Use of [RH052 trade name] is contraindicated where pregnancy has not been confirmed by gynaecological examination, ultrasound or biochemical tests, or where there is a known or suspected ectopic pregnancy.

Use is also contraindicated if the patient is hypersensitive to the active ingredients or any of the excipients listed in section 6.1, and in the following situations:

- Adrenal failure
- Hypersensitivity to any other medicines required for use in combination with [RH052 trade name]
- Severe asthma uncontrolled by therapy
- Inherited porphyria.

4.4 Special warnings and precautions for use

Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see section 4.8). In patients who experience severe cutaneous adverse reactions, treatment with mifepristone should be immediately discontinued. Re-treatment with mifepristone is not recommended.

Pregnancy-related symptoms such as nausea and vomiting may increase after mifepristone and misoprostol administration but will decrease and disappear during the abortion process.

In the absence of relevant studies, [RH052 trade name] is not recommended in women with:

- malnutrition
- severe renal impairment
- hepatic failure

Caution and clinical judgement are required for individuals receiving corticosteroids long term, and for those who have bleeding disorders or severe anaemia.

Abortion induction

The age of the pregnancy must be determined from the history and clinical examination of the patient. Uterine ultrasound is recommended.

Tests for Rhesus (Rh) blood group typing should be provided when feasible, so that Rh- immunoglobulin can be given for the prevention of rhesus allo-immunisation where indicated.

Limited data are available for the use of mifepristone with misoprostol in patients under 18 years of age. [RH052 trade name] should not be used in children below pubertal age.

Before providing [RH052 trade name], women who have undergone genital mutilation must undergo a physical examination by a qualified health care practitioner to rule out any anatomical obstacles to medical termination of pregnancy.

In the case of a pregnancy occurring despite an intra-uterine device in situ, this device must be removed before administration of [RH052 trade name].

Medical termination of intra-uterine pregnancy with [RH052 trade name] requires the active involvement of the patient, who should be informed of the method's requirements and the possibility of failure, requiring termination of pregnancy by another method. Efficacy decreases with parity and increasing age of the patient, and in the rare case of incomplete expulsion, surgical treatment may be necessary.

Patients should receive oral and written instructions about how to care for themselves after the procedure. These instructions should include how much bleeding to expect, how to recognise potential complications, and how and where to seek help if required.

A follow-up visit within 7 to 14 days after taking [RH052 trade name] may be required, depending on the clinical situation.

Expulsion of products of conception may take place before administration of the misoprostol tablets (in about 3% of cases).

Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 9 to 13 days after administration of [RH052 trade name] and misoprostol) which may be heavy. Bleeding occurs in almost all cases and is not a proof of complete expulsion; persistent bleeding beyond about 14 days may indicate incomplete abortion or an undiagnosed ectopic pregnancy.

Infection

Any existing reproductive-tract infections should be treated before [RH052 trade name] is given.

The reproductive 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. Many of the symptoms of pelvic infection, such as pain, are often non-specific and hence precise diagnosis is difficult. In women with clinical signs such as pelvic pain, abdominal or adnexal tenderness, vaginal discharge and fever, a pelvic infection should be suspected and appropriate treatment should be given.

Serious cases (including fatal cases) of toxic shock and septic shock caused by atypical pathogens like *Clostridium sordellii* and *C. perfringens*, *Klebsiella pneumoniae* and *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. Health care providers should be aware of this potentially fatal complication.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicines on mifepristone

Levels of mifepristone may increase if given with inhibitors of CYP3A4 including, but not limited to:

- Ketoconazole
- Itraconazole
- Erythromycin
- Grapefruit juice

However, the change in mifepristone exposure is not considered likely to be clinically relevant, and no adjustment of mifepristone dose is required when given concomitantly with a CYP3A4 inhibitor.

Levels of mifepristone may be reduced if given with inducers of CYP3A4 including, but not limited to:

- Rifampicin
- Dexamethasone
- St. John's wort
- Certain antiepileptic medicines including phenytoin, phenobarbital and carbamazepine.

Dose adjustment of mifepristone may be needed in a patient treated concomitantly with strong or moderate CYP3A4 inducers. In such circumstances, a single oral dose of mifepristone 600 mg (i.e. 3 tablets of 200 mg), followed 36 to 48 hours later by the administration of the prostaglandin analogue, has been recommended for induction of abortion.

Effect of mifepristone on other medicines

Based on in vitro inhibition information, co-administration of mifepristone may increase serum levels of drugs that are CYP3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may occur 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 ciclosporin, tacrolimus, sirolimus, everolimus, alfentanil, dihydroergotamine, ergotamine, fentanyl, quinidine, and some agents used during general anaesthesia.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Birth defects or malformations have occurred in ongoing pregnancies exposed to mifepristone.

Patients considering medical termination of pregnancy should be counselled on the risks to the fetus if termination with [RH052 trade name] plus misoprostol fails and a second termination of pregnancy procedure is not desirable. Data on a potential risk of fetal abnormality after an unsuccessful medical abortion are limited and inconclusive; therefore, it is unnecessary to insist on termination of an exposed pregnancy if the patient wishes to continue it. However:

- If the patient still wishes to terminate the pregnancy, then another method should be used.
- If the patient wishes to continue with the pregnancy, appropriate follow-up is needed. A careful ultrasound monitoring of the pregnancy in a specialised centre is recommended, with special attention to the limbs and head.

Patients who wish to become pregnant again should be advised to avoid doing so before their next period after taking [RH052 trade name], in order to allow mifepristone to be cleared from the body.

Breastfeeding

Mifepristone is present in breast milk in small amounts. Patients who are still breastfeeding another child should be told not do so for a week after the dose of [RH052 trade name]

Fertility

Adverse effects on fertility in humans have not been seen. Women are able to become pregnant again soon after termination of pregnancy with mifepristone and misoprostol. Where appropriate, the patient should avoid unprotected intercourse and start contraception immediately after successful termination of the pregnancy.

4.7 Effects on ability to drive and use machines

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

[RH052 trade name] may cause dizziness. Patients should be advised that if they experience these symptoms, they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

The adverse reactions below have been attributed to mifepristone, or to mifepristone-based abortion induction; since mifepristone is typically followed by use of a prostaglandin such as misoprostol, the adverse effects of the latter should also be considered.

Adverse reactions are listed below by body system or organ. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10) uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Nervous system disorders	
Common	headache, fainting/dizziness
Immune system disorders	
Not known	anaphylaxis, hypersensitivity
Gastrointestinal disorders	
Very common	nausea, vomiting, diarrhoea
Common	cramping
Skin and subcutaneous tissue disorders	
Uncommon	rash
Rare	urticaria, erythroderma, erythema nodosum, toxic epidermal necrolysis
Very rare	angioedema
Vascular disorders	
Uncommon	hypotension
Very rare	cardiovascular events (myocardial infarction, coronary artery spasm, severe hypotension)
Musculoskeletal and connective tissue disorders	
Not known	back pain
Infections and infestations	
Common	infection following abortion (<5%); endometritis; pelvic inflammatory disease
Very rare	fatal toxic shock syndrome (see section 4.4)
Reproductive system disorders	
Very common	uterine contractions and cramping (10-45%) in the hours after misoprostol administration
Common	heavy bleeding (in about 5% of cases; may require haemostatic curettage in up to 1.4% of cases)

Rare	uterine rupture after misoprostol (see section 4.4)

Congenital, familial, and genetic disorders

Common	fetal malformations

General disorders and administration site disorders

Very common	shivering, fever (including temperatures ≥40°)
Common	chills
Uncommon	fatigue
Rare	malaise; vagal symptoms (e.g. hot flushes, dizziness)

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

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 / anti-progestogen.

ATC code: GO3XB01.

Mifepristone is a synthetic steroid with an antiprogestational 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). This action is manifested in the form of pregnancy termination in rodents.

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. The effect is greatest when a prostaglandin is administered 36 to 48 hours after mifepristone.

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 per cent of the cases and accelerates the expulsion of the conceptus.

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 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 of [RH052 trade name]

The absorption characteristics of [RH052 trade name] have been determined after administration of one mifepristone 200 mg tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**
Maximum concentration (C_{max})	2.32 ± 0.85 µg /mL
Area under the curve (AUC_{0-t}), a measure of the extent of absorption	42.3 ± 17.5 µg·h/mL
Time to attain maximum concentration (tmax)	1.47 ± 2.70 h

Pharmacokinetics of mifepristone

Absorption	
Absolute bioavailability	After oral administration of low doses of mifepristone (20 mg), the absolute bioavailability is 69%.
Oral bioavailability	69%
Food effect	NA
Distribution	
General note	Due to specific and saturable binding to alpha-1-acid glycoprotein (AAG), the volume of distribution and plasma clearance are inversely proportional to the plasma concentration of AAG.
Volume of distribution (mean)	0.4 - 1.47 L/kg
Plasma protein binding	98% bound to albumin and AAG (saturable)
Tissue distribution	NA
Metabolism	
General	Hepatic metabolism. CYP3A4
Active metabolite(s)	None.
Elimination	
Elimination half-life	25 - 30 h
Mean systemic clearance (Cl/F)	0.55 L/kg/day
% of dose excreted in urine	10%
% of dose excreted in faeces	90%
Pharmacokinetic linearity	At doses over 100 mg mifepristone exhibits non-linear pharmacokinetics due to saturation of binding to AAG

Metabolizing enzymes	Substrate and inhibitor of CYP450 3A4
Special populations	
Renal impairment	NA
Hepatic impairment	NA
Elderly patients	NA
Paediatric patients	NA

Special populations

Hepatic impairment

A study compared 8 women with moderate hepatic impairment and 8 women with normal hepatic function, treated with a single oral dose of mifepristone 200 mg to assess the pharmacokinetics of mifepristone and its metabolites (N demethylated metabolite, hydroxylated metabolite and di-demethylated metabolite).

The total C_{max} of mifepristone and its metabolites were reduced by half in patients with moderate hepatic impairment versus the women with normal hepatic function. Similarly, the total AUC_{∞} was reduced by 43% and 50% for mifepristone and N-demethylated metabolite in patients with moderate hepatic impairment. This decrease in exposure could be caused by a decrease in absorption and/or protein binding. However, assessment of mifepristone and its metabolites unbound fractions (0.2 to 6%) could not be performed with enough accuracy to demonstrate any significant variation between the two groups, and the clinical relevance, if any, is uncertain.

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 (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In reproductive toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving fetal exposure. In rabbits surviving fetal exposure, however, fetal anomalies were observed (cranial vault, brain and spinal cord). The effect was dose-dependent. In monkeys, the number of fetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment. No evidence of teratogenicity was observed in postimplantation 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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light. Store in the original package.

6.5 Nature and contents of container

White and non-transparent plastic (PVC) on aluminium foil blister cards, each containing 1 or 3 tablets. Available in boxes of 1×1 or 1×3 tablets.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH052

9. DATE OF PREQUALIFICATION

15 August 2016

10. DATE OF REVISION OF THE TEXT

May 2025

References

Mifegyne 200 mg tablets: summary of product characteristics. MHRA; 21 Feb 2025 (https://mhraproducts4853.blob.core.windows.net/docs/986fa9aa372685a127196dd7803940f1f94e2be7, accessed 16 March 2025)

Clinical practice handbook for quality abortion care . Geneva: World Health Organization; 2023 (https://iris.who.int/bitstream/handle/10665/369488/9789240075207-eng.pdf?sequence=1, accessed 16 March 2025)

Abortion care guideline. Geneva: World Health Organization; 2022. (https://iris.who.int/bitstream/handle/10665/349316/9789240039483-eng.pdf?sequence=1, accessed 16 March 2025)

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products