# เอกสารกำกับยาภาษาอังกฤษ

## 1. NAME OF THE MEDICINAL PRODUCT

MISOMIFE-FEM COMBO

Co-package of Mifepristone 200 mg Tablets and Misoprostol 4×200 mcg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The co-blistered combination comprises:

mifepristone 200 mg tablets

misoprostol 200 mcg vaginal tablets

For a full list of excipients see 6.1.

## 3. PHARMACEUTICAL FORM

*Mifepristone 200 mg tablets*

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

*Misoprostol 200 mcg vaginal tablets*

Hexagonal white tablets, debossed with M and 3 at each side of a score line on the flat side, the other side is slightly convex.

The score line is not intended for breaking the tablet. The vaginal tablet should not be divided.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

MISOMIFE-FEM COMBO is indicated for the management of induced abortion.

It should be prescribed and administered in accordance with countries' national laws and regulations.

### 4.2 Posology and method of administration

**Medical management of induced abortion at less than 12 weeks of gestation:**

200 mg of mifepristone (i.e. 1 tablet of 200 mg) is taken as a single oral dose under the supervision of a health care provider, followed 1 to 2 days later by 800 mcg of misoprostol (i.e. 4 × 200 mcg tablets) by the vaginal, buccal or sublingual route.

**Medical management of induced abortion at 12 weeks of gestation or later:**

200 mg of mifepristone (i.e. 1 tablet of 200 mg) is taken as a single oral dose under the supervision of a health care provider, followed 1 to 2 days later by 400 mcg of misoprostol (i.e. 2 × 200 mcg tablets) preferably by the vaginal route but buccal or sublingual route may also be used. An additional dose of 400 mcg of misoprostol should be given three hours later.

Further doses of 400 mcg of misoprostol may be given every three hours if required.

*Method of administration:*

The mifepristone 200 mg tablet should be swallowed whole and not broken or crushed.

The vaginal route is preferred for misoprostol; however, the buccal or sublingual route may also be used. Misoprostol tablets are placed in the vaginal fornices (deepest portions of the vagina) and the woman should

continue lying down for 30 minutes. For buccal use, misoprostol tablets are placed between the cheek and gums and swallowed after 30 minutes; for sublingual use, the tablets are placed under the tongue and swallowed after 30 minutes.

*Hepatic and renal failure:*

Mifepristone 200 mg tablets are not recommended in patients with severe hepatic or renal disease due to the lack of data. An alternative method of pregnancy termination should be considered in these populations.

*Paediatric population:*

Limited data are available for women under 18 years of age.

**4.3 Contraindications**

MISOMIFE-FEM COMBO for medical termination of developing pregnancy is contraindicated in the following situations:

- Adrenal failure
- Hypersensitivity to the active ingredients or any of the excipients listed in section 6.1
- Severe asthma uncontrolled by therapy
- Inherited porphyria
- Pregnancy not confirmed by gynaecological examination, ultrasound or biochemical tests
- Known or suspected ectopic pregnancy

**4.4 Special warnings and precautions for use**

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

Before providing MISOMIFE-FEM COMBO, 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 with an intra-uterine device in situ, this device must be removed before administration of MISOMIFE-FEM COMBO.

Medical termination of developing intra-uterine pregnancy with MISOMIFE-FEM COMBO requires the active involvement of the woman, who should be informed of the method's requirements:

- The need to use both components of the treatment including the administration of misoprostol vaginal tablets 1 to 2 days after administration of the mifepristone 200 mg tablet
- The possibility of failure of MISOMIFE-FEM COMBO, requiring termination of pregnancy by another method.

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 recognise potential complications, and how and where to seek help if required.

A follow-up visit within 7 to 14 days after taking MISOMIFE-FEM COMBO may be required, depending on the clinical situation.

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

Risks related to the procedure:

*Failure:*

- Failure occurs in 1.3 to 7.5% of cases
- In the rare case of incomplete expulsion, surgical treatment may be necessary
- The efficacy of the method decreases with parity and 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 administration of MISOMIFE-FEM COMBO) which may be heavy. Bleeding occurs in almost all cases and is not a proof of complete expulsion.

*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 decrease and disappear during the abortion process.

Any reproductive tract infections should be treated before MISOMIFE-FEM COMBO is given.

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.

Rare but serious cardiovascular events have been reported in association with administration of a prostaglandin analogue for medical termination of pregnancy. Women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

*Follow-up visit:*

Following uncomplicated surgical and medical abortion using MISOMIFE-FEM COMBO, 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.

**4.5 Interaction with other medicinal products and other forms of interaction**

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

- Ketoconazole
- Itraconazole
- Erythromycin
- Grapefruit juice

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

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

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.

No significant interactions are anticipated with the administration of misoprostol.

**4.6 Fertility, pregnancy and breastfeeding**

*Pregnancy*

Birth defects or malformations have occurred in ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone. Prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis, with or without limb defects) and with amniotic band syndrome (leading to limb deformities/amputations such as clubfoot, acheiria, oligodactyly, or other potential defects including cleft palate).

Women considering medical termination of pregnancy should be counselled on the risks to the fetus if termination with MISOMIFE-FEM COMBO fails and a second termination of pregnancy procedure is not desirable. Consequently:

- If the medical induction of abortion fails and the woman still wishes to terminate the pregnancy, then another method should be used.
- If the woman wishes to continue with her pregnancy, a careful ultrasound monitoring of the pregnancy, with a special attention to the limbs, must be established in a specialised centre.

*Breastfeeding*

Mifepristone and misoprostol are present in breast milk in small amounts. Women should avoid breastfeeding while taking mifepristone and misoprostol.

*Fertility*

The use of the combination of mifepristone and misoprostol for early termination was not associated with subsequent impairment of fertility. A woman can become pregnant again as soon as the termination of

pregnancy is completed. Therefore, it is important to inform the patient to start contraception immediately after the termination of the pregnancy is confirmed.

From fertility and early embryonic development studies in rats, there is evidence of a possible adverse effect of misoprostol on implantation; however, this is not relevant for the indicated clinical use of MISOMIFE-FEM COMBO (see Section 5.3).

**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. The active ingredients of MISOMIFE-FEM COMBO may cause dizziness and tiredness. Women should be instructed that if they experience these symptoms, they should avoid potentially hazardous tasks such as driving and operating machinery.

**4.8 Undesirable effects**

The following adverse events (AEs) have been reported with the use of MISOMIFE-FEM COMBO with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

| System organ class | Very common | Common | Uncommon | Rare | Very rare |
|---|---|---|---|---|---|
| **General disorders** | Shivering; fever including temperature > 40° C | Chills | Fatigue | Malaise; vagal symptoms (hot flushes, dizziness, chills) | |
| **Nervous system disorders** | | Headache; fainting; dizziness | | | |
| **Gastrointestinal disorders** | Nausea; vomiting; diarrhoea | Cramping | | | |
| **Skin and subcutaneous tissue disorders** | | | Hypersensitivity; rash (0.25%) | Urticaria; erythroderma; erythema nodosum; toxic epidermal necrolysis | Angioedema |
| **Vascular disorders** | | | Hypotension | | Cardiovascular events (myocardial infarction, coronary artery |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | spasm, severe hypotension) |
| **Infections and infestations** | | Infection following abortion (<5%); endometritis; pelvic inflammatory disease | | | Fatal toxic shock syndrome (see section 4.4) |
| **Reproductive system disorders** | Uterine contractions and cramping (10-45%) in the hours after misoprostol administration | Heavy bleeding* | | Uterine rupture** | |

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

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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

**4.9 Overdose**

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

Symptoms linked to overdose of misoprostol are fever, blood pressure disorders, nausea, abdominal cramping and tremors. There is no known antidote for misoprostol overdose. In the event of an overdose, the patient should be closely monitored.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

**Mifepristone**

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

ATC code: G03XB01

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

In women at doses of at least 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction-inducing action of prostaglandins. The effect is greatest when a prostaglandin is administered 36 to 48 hours after mifepristone.

Mifepristone induces softening and dilatation of the cervix, which are detectable from 24 hours after administration of mifepristone and increase to a maximum after approximately 36-48 hours.

Mifepristone binds to the glucocorticoid receptor. 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 may be reduced for several days following a single administration of 200 mg mifepristone for termination of pregnancy. The clinical implications of this are unclear, but vomiting and nausea may be increased in susceptible women.

**Misoprostol**

Pharmacotherapeutic group: Other gynaecologicals, prostaglandins.

ATC code: G02AD06

Misoprostol is a synthetic analogue of prostaglandin E1. 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 facilitate cervical dilatation and evacuation of the product of conception. 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 four hours after vaginal administration. Vaginal administration of misoprostol induces far more powerful and regular contractions than does oral administration.

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.

**5.2 Pharmacokinetic properties**

*Absorption of MISOMIFE-FEM COMBO*

| **Pharmacokinetic variable** | **Mean value* (± standard deviation)** | | | |
|---|---|---|---|---|
| | **Mifepristone 200 mg orally** | **Misoprostol 400 mcg orally** | **Misoprostol 800 mcg vaginally** | **Misoprostol 800 mcg orally** |
| Maximum concentration ($C_{max}$) | 2.32 ± 0.85 µg/mL | 1.08 ± 0.43 ng/mL | 1.02 ± 0.61 ng/mL | 2.69 ± 1.22 ng/mL |
| Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption | 42.3 ± 17.5 µg·hour/mL | 0.66 ± 0.24 ng·hour/mL | 5.98 ± 5.65 ng·hour/mL | 2.18 ± 0.53 ng·hour/mL |
| Time to attain maximum concentration ($t_{max}$) | 1.47 ± 2.70 hours | 12 (range: 7.5 - 60) minutes | 1.5 (range: 1.0 - 24) hours | 0.33 (range: 0.20 - 0.67) hour |
| * arithmetic mean | | | | |

*Pharmacokinetics of mifepristone and misoprostol*

| | **Mifepristone** | **Misoprostol** |
|---|---|---|
| **General** | | |
| | | Misoprostol is rapidly and completely de-esterified to |

| | Mifepristone | Misoprostol |
|---|---|---|
| | | pharmacologically active misoprostol acid in the liver. It is almost undetectable in plasma after oral administration. Bioavailability is greater when given by the buccal, sublingual or vaginal route |
| **Absorption** | | |
| Absolute bioavailability | 69% (20 mg dose) | NA |
| Oral Bioavailability | At least 69% | Approximately 7% |
| Food effect | | ↓ $C_{max}$, ↔ AUC (oral administration) |
| **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 | 0.4 - 1.47 L/kg | Approximately 14 L/kg (active metabolite) |
| Plasma protein binding *in vitro* | 98% bound to albumin and AAG (saturable) | < 90% misoprostol, 85% active metabolite |
| Tissue distribution | NA | NA |
| **Metabolism** | | |
| | CYP3A4 | de-esterification |
| **Elimination** | | |
| Elimination half-life | 25 - 30 h | 13 - 40 min (active metabolite) |
| Mean systemic clearance (Cl/F) | 0.55 L/kg/day | Approximately 0.29 L/kg/min (active metabolite) |
| % of dose excreted in urine | 10% | 73% |
| % of dose excreted in faeces | 90% | 15% |
| **Pharmacokinetic linearity** | At doses > 100 mg mifepristone exhibits non-linear pharmacokinetics due to saturation of binding to AAG | NA |

| | Mifepristone | Misoprostol |
|---|---|---|
| **Drug interactions (in vitro)** | | |
| Metabolising enzymes | Substrate and inhibitor of CYP3A4 | |
| **Special populations** | | |
| Renal impairment | NA | No dose changes are required for any degree of renal impairment |
| Hepatic impairment | NA | Severe hepatic impairment may alter pharmacokinetics. |
| Elderly patients | NA | NA |
| Paediatric patients | NA | NA |

**5.3 Preclinical safety data**

**Mifepristone:**

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 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 fetuses 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.

**Misoprostol:**

Single dose toxicity studies in rodents and non-rodents 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 after repeated dosing.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

*Mifepristone tablet*

Colloidal silicon dioxide

Corn starch

Povidone

Magnesium stearate

Microcrystalline cellulose

*Misoprostol tablet*

Microcrystalline cellulose

Sodium starch glycolate

Hydrogenated castor oil

Hypromellose (HPMC)

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

24 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**

1 tablet of mifepristone and 4 vaginal tablets of misoprostol are packed in an alu/alu blister. Each blister is supplied in a carton.

**6.6 Instructions for use and handling and disposal**

No special requirements.

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

**7. Manufacturer and Marketing Authorization Holder**

Manufacturer:

China Resources Zizhu Pharmaceutical Co. Ltd

No. 27, Chaoyang North Road, Chaoyang District, Beijing 100024, People's Republic of China

Importer:

The R Solutions Co., Ltd.

28 Teka Building, 4th Fl., Ngamwongwan Road, Soi 6, Bang Khen, Muang, Nonthaburi 11000

**8. WHO PREQUALIFICATION**

REFERENCE NUMBER: RH089

DATE OF PREQUALIFICATION: 19 November 2019

**9. DATE OF REVISION**

March 2020