					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