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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH089 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The co-blistered combination comprises:

mifepristone 200 mg tablets

misoprostol 200 µg tablets

For a full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Mifepristone 200mg tablets

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

Misoprostol 200µg 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 tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH089 trade name] is indicated for the induction of abortion. It may also be used for the management of missed abortion and intrauterine fetal death.

Decisions on the appropriate use of [RH089 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. Extra tablets of misoprostol 200 µg should therefore be available in case they are needed.

† 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. Tablets of misoprostol 200 µg should therefore be available if required for use in addition to those included with [RH089 trade name].

Renal impairment

Mifepristone 200 mg tablets are not recommended in patients with severe renal impairment due to lack of data.

Hepatic impairment

In the absence of relevant studies, [RH089 trade name] is not recommended in women with hepatic failure.

Method of administration

The **mifepristone** 200-mg tablet is taken *orally*. It 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.

For *vaginal* administration, misoprostol tablets are inserted into the vaginal fornices (deepest portions of the vagina) and the patient should continue lying down for 30 minutes.

For *buccal* use, patients should be instructed to place misoprostol tablets between the cheek and gums for 20 to 30 minutes and then swallow any remainder.

For *sublingual* use, patients should be instructed to place the misoprostol tablets under the tongue for 30 minutes and then swallow any remainder.

4.3 Contraindications

Use of [RH089 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
- Allergy to prostaglandins
- 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.

Misoprostol should be used with caution in patients with heart disease or cardiovascular risk factors (e.g. age over 35 years, long-term smoker, hyperlipidaemia, and diabetes), because cardiovascular events (e.g.

myocardial infarction, coronary artery spasm, and severe hypotension) have been reported in association with misoprostol.

In the absence of relevant studies, [RH089 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.

Health care providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in individuals who have undergone prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered.

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. [RH089 trade name] should not be used in children below pubertal age.

Before providing [RH089 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 [RH089 trade name].

Medical termination of intra-uterine pregnancy with [RH089 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 [RH089 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 [RH089 trade name]) 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 [RH089 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

nonspecific 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.

4.5 Interaction with other medicinal products and other forms of interaction

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, and therefore an alternative product may be needed rather than [RH089 trade name].

Effect 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.

Misoprostol

No interactions between misoprostol and oxytocin have been reported in women exposed to prophylactic oxytocin (intramuscular or intravenous) before administration of misoprostol.

Misoprostol is mainly metabolised through fatty acid oxidising systems and has shown no adverse effect on the hepatic microsomal mixed function oxidase (P450) enzyme system. Misoprostol does not change the pharmacokinetics of antipyrine, suggesting that it does not induce hepatic enzymes.

Interaction studies showed that the pharmacokinetics of propranolol and diazepam are not influenced by concomitant administration of misoprostol.

Combination with non-steroidal anti-inflammatory drugs

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

Antacids

In a small study, co-administration of misoprostol with antacid reduced the bioavailability of misoprostol acid (the active metabolite of misoprostol) by 16%. Clinical trials of misoprostol with concomitant antacid use suggest that this effect is not clinically important.

Antacids containing magnesium could potentially aggravate diarrhoea caused by 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 leading to hypomimia, problems suckling and swallowing, and abnormal eye movements, with or without limb defects) and with amniotic band syndrome (leading to limb deformities/amputations such as clubfoot, acheiria, olygodactyly, and cleft palate), and other central nervous system abnormalities such as neural tube defects. Patients considering medical termination of pregnancy should be counselled on the risks to the fetus if termination with [RH089 trade name] 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.

Breastfeeding

Mifepristone is present in breast milk in small amounts.

The levels of misoprostol in breast milk are low and decline very rapidly: 5 hours after a single oral dose of 600 µg of misoprostol, the levels in breast milk are unmeasurable.

Fertility

Adverse effects on fertility in humans have not been seen. Women are able to become pregnant again soon after termination of pregnancy with [RH089 trade name]. Where appropriate, the patient should avoid unprotected intercourse and start contraception immediately after successful termination of the pregnancy.

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 [RH089 trade name] (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 [RH089 trade name] may cause dizziness and tiredness. 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

Summary of the safety profile

The most commonly reported adverse reactions during treatment are shivering and fever. In general, shivering and fever occur 60 to 90 minutes after misoprostol administration and are transient and short-lived. Gastrointestinal side effects such as nausea, vomiting, diarrhoea and abdominal pain are also reported commonly.

Tabulated list of adverse reactions

The adverse reactions reported in the clinical program are provided in the table below and are classified according to system organ class with the following frequencies: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the 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

[RH089 trade name] supplies only a single dose of mifepristone, so overdose is unlikely. In the event of 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 and appropriate symptomatic care should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mifepristone

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

ATC code: G03XB51

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 1 mg/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 E_1. 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 4 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% of the cases and accelerates the expulsion of the conceptus.

5.2 Pharmacokinetic properties

Absorption of [RH089 trade name]

Pharmacokinetic variable	**Mean value* (± standard deviation)**			
	Mifepristone 200 mg orally	**Misoprostol 400 µg orally**	**Misoprostol 800 µg vaginally**	**Misoprostol 800 µg 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	39.6 ± 14.6 ng·min/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 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		↓ Cmax, ↔ 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 over 100 mg mifepristone exhibits non-linear pharmacokinetics due to saturation of binding to AAG	NA
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

NA: data not available/not applicable

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 fetal 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 postimplantation 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 200 mg and 4 tablets of misoprostol 200 µg are packed in an Alu/Alu blister. Each blister is supplied in a carton.

6.6 Special precautions for disposal and other handling No special requirements.

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 (WHO Prequalification Programme)

RH089

9. DATE OF PREQUALIFICATION

19 November 2019

10. DATE OF REVISION OF THE TEXT

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References

1. WHO. Abortion care guideline. Geneva; 2022. Available at: https://apps.who.int/iris/rest/bitstreams/1394380/retrieve (accessed 09/22).
2. WHO. WHO Recommendations on maternal health: Guidelines approved by the WHO Guidelines Review Committee, updated May 2017. Available at: https://apps.who.int/iris/rest/bitstreams/1090523/retrieve (accessed 09/22).
3. UK Summary of product characteristics. Medabon (mifepristone + misoprostol) Available at: https://www.medicines.org.uk/emc/product/3380 [Accessed 09/22]
4. UK Summary of product characteristics. Mifegyne (mifepristone) Available at: https://www.medicines.org.uk/emc/product/3783 [Accessed 01/23]
5. UK Summary of product characteristics. Topogyne (misoprostol) Available at: https://www.medicines.org.uk/emc/product/3234 [Accessed 09/22]
6. Schaff EA, DiCenzo R, Fielding SL. Comparison of misoprostol plasma concentrations following buccal and sublingual administration. *Contraception* 2005; **71:** 22-25. Available at: https://doi.org/10.1016/j.contraception.2004.06.014 (accessed 09/22).
7. Middleton T, Schaff E, Fielding SL, *et al.* Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005; **72:** 328-32. Available at: https://doi.org/10.1016/j.contraception.2005.05.017 (accessed 09/22).
8. Meckstroth KR, Whitaker AK, Bertisch S, *et al.* Misoprostol administered by epithelial routes: drug absorption and uterine response. *Obstet Gynecol* 2006; 108: 582-90. Available at https://doi.org/10.1097/01.aog.0000230398.32794.9d (accessed 09/22).
9. Raghavan S, Comendant R, Digol I, *et al.* Comparison of 400 mcg buccal and 400 mcg sublingual misoprostol after mifepristone medical abortion through 63 days' LMP: a randomized controlled trial. *Contraception* 2010; **82:** 51319. Available at: https://doi.org/10.1016/j.contraception.2010.05.013 (accessed 09/22).
10. Chai J, Wong CYG, Ho PC. A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation. *Contraception* 2013; **87:** 480-5. Available at: https://doi.org/10.1016/j.contraception.2012.09.022 (accessed 09/22).
11. Alfirevic Z, Aflaifel N, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev 2014 Jun 13;2014(6):CD001338. Available at: https://doi.org/10.1002/14651858.cd001338.pub3 (accessed 09/22).
12. Garg G, Takkar N, Sehgal A. A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation. *J Obstet Gynaecol India* 2015; **62:** 111-16. Available at: https://doi.org/10.1007/s13224-014-0605-5 (accessed 09/22).
13. Wu H-L, Marwah S, Wang P, et al. Misoprostol for medical treatment of missed abortion: a systematic review and network meta-analysis. Sci Rep 2017; 7: 1644. Available at: https://doi.org/10.1038/s41598-017-01892-0 (accessed 09/22).
14. Kerr RS, Kumar N, Williams MJ, et al. Low-dose oral misoprostol for induction of labour. *Cochrane Database Syst Rev* 2021 Jun 22;6(6):CD014484. Available at: https://doi.org/10.1002/14651858.cd014484 (accessed 09/22).