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

[RH056 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains 200 µg of misoprostol.

Excipient with known effect

Each tablet contains 1 mg of hydrogenated castor oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white, round, biconvex, uncoated tablets, plain on both sides.

The tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH056 trade name] is indicated for induction of labour at term. It may also be used to induce labour in the third trimester of pregnancy after death of the fetus or where there is a fetal anomaly.

[RH056 trade name] is indicated for prevention of postpartum haemorrhage when oxytocin is not available. It may also be used to treat established postpartum haemorrhage if oxytocin cannot be given or is not effective.

[RH056 trade name] is indicated in combination with mifepristone or letrozole, or used alone, for the induction of abortion. It may also be used alone for cervical priming before surgical abortion.

[RH056 trade name] is also used for incomplete abortion, and with mifepristone or alone for the management of missed abortion and intrauterine fetal death.

Decisions on the appropriate use of [RH056 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 labour at term, or in the third trimester (with a fetal anomaly or after intrauterine death)

For induction of labour, women may be given 25 µg misoprostol *orally* every 2 hours, until start of labour. If labour has not ensued after 8 doses (200 µg misoprostol in total) have been given, the patient should be re-evaluated.

In order to supply such doses a tablet of [RH056 trade name] should be dispersed in water and a portion of the resulting mixture given for each dose, as described under 'Method of administration', below.

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

Postpartum haemorrhage

Prevention

When oxytocin is not available or cannot be used, a single *oral* dose of misoprostol 400 or 600 µg (2 or 3 [RH056 trade name] tablets) may be given for prevention of postpartum haemorrhage.

Tablets should be swallowed whole and not broken or crushed.

Treatment

When oxytocin is not available, or bleeding does not respond to oxytocin, a single dose of misoprostol 800 µg (4 [RH056 trade name] tablets) may be given by the *sublingual* route.

Induction of abortion

When used for induction of medical abortion (termination of pregnancy) in line with relevant guidelines and national regulations, one of the following regimens may be used, depending on duration of gestation and on whether [RH056 trade name] is to be used with other medicines or as monotherapy.

At less than 12 weeks:

With mifepristone

Treatment should begin with a single dose of mifepristone 200 mg *orally*, followed after 24 to 48 hours by misoprostol 800 µg (4 [RH056 trade name] tablets) by the *vaginal, sublingual* or *buccal* route.

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

As monotherapy

Misoprostol may be given alone in a dose of 800 µg (4 [RH056 trade name] tablets) by the *vaginal, sublingual* or *buccal* route.

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

With letrozole

If [RH056 trade name] is used in a regimen with letrozole, treatment should begin with letrozole 10 mg once daily *orally* for 3 days, followed on the fourth day by misoprostol 800 µg (4 [RH056 trade name] tablets) by the *sublingual* route.

At 12 weeks or more:

With mifepristone

Treatment should begin with a single dose of mifepristone 200 mg *orally*, followed after 24 to 48 hours by misoprostol 400 µg (2 [RH056 trade name] tablets) by the *vaginal, sublingual* or *buccal* route every 3 hours as needed, until abortion is successful.

As monotherapy

When it cannot be given with mifepristone, misoprostol may be given alone in a dose of 400 µg (2 [RH056 trade name] tablets) by the *vaginal, sublingual* or *buccal* route every 3 hours as needed, until abortion is successful.

Cervical priming before surgical abortion

Where surgical abortion is to be performed at less than 12 weeks gestation, misoprostol 400 µg (2 [RH056 trade name] tablets) may be given for cervical priming before the procedure by one of the following routes:

sublingual route, given 1 to 2 hours before the procedure

vaginal or *buccal* route, given 2 to 3 hours before the procedure.

If misoprostol is used for cervical priming before surgical abortions at later gestational ages, it should be combined with mifepristone or an osmotic dilator or both.

Incomplete abortion

For the medical management of incomplete abortion (either induced or spontaneous), the choice of regimen depends on the duration of gestation.

Less than 14 weeks:

Oral route: misoprostol 600 µg (3 [RH056 trade name] tablets) as a single dose

Sublingual route: misoprostol 400 µg (2 [RH056 trade name] tablets) as a single dose.

14 weeks or more:

Vaginal, sublingual, or *buccal route:* misoprostol 400 µg every 3 hours, repeated until abortion is successful.

Missed abortion

Where medical management is considered appropriate for missed abortion at gestational ages less than 14 weeks, patients should receive a single dose of mifepristone 200 mg *orally*, followed after at least 24 hours by misoprostol 800 µg (4 [RH056 trade name] tablets) by the *vaginal*, *sublingual* or *buccal* route.

If mifepristone cannot be given, misoprostol may be given alone. Doses of 800 µg should be repeated as necessary for successful abortion. At gestational ages ≥9 weeks, evidence shows that repeat dosing of misoprostol is more effective in achieving successful abortion.

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 [RH056 trade name] tablets) by the *sublingual* or *vaginal* route every 4 to 6 hours as needed, until abortion is successful.

Renal impairment

No dose adjustment is required (see section 5.2).

Hepatic impairment

No dose adjustment is required in mild to moderate hepatic impairment (see section 5.2). In the absence of relevant studies, [RH056 trade name] is not recommended in women with hepatic failure.

Method of administration

Oral route

When given orally, the tablets should be swallowed whole to ensure administration of the complete dose; they should not be broken or crushed.

Concomitant ingestion of food decreases the bioavailability of oral misoprostol. Therefore, misoprostol should preferably be taken on an empty stomach. However, it can be given without consideration of food intake if needed in life-threatening situations.

Other routes

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

When administered *sublingually*, patients should be instructed to place tablets under the tongue for 30 minutes and then swallow any remainder.

For *vaginal* administration, tablets of [RH056 trade name] are inserted into the vaginal fornices (deepest portions of the vagina) and the patient should continue lying down for 30 minutes

4.3 Contraindications

- Hypersensitivity to misoprostol or to any of the excipients listed in section 6.1
- Hypersensitivity to any other medicines required for use in combination with [RH056 trade name]
- Allergy to prostaglandins

Contraindications in abortion setting:
The following conditions are contraindications for misoprostol use in termination of pregnancy:

- Inherited porphyria
- Adrenal failure
- Pregnancy not confirmed by gynaecological examination, ultrasound or biochemical tests
- Known or suspected ectopic pregnancy

4.4 Special warnings and precautions for use

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), as 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, misoprostol is not recommended in women with:

- malnutrition
- hepatic failure

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

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

When used for induction of labour the mother and baby should be closely monitored immediately after misoprostol is given.

In general, misoprostol is not recommended for labour induction in women with a scarred uterus (e.g. due to previous caesarean section). For other procedures at later gestational ages, 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.

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 misoprostol in patients under 18 years of age. [RH056 trade name] should not be used in children below pubertal age.

Abortion induction

Before providing [RH056 trade name], women who have undergone genital mutilation must be examined by a qualified health care provider experienced in managing obstetric complications, to rule out any anatomical obstacles to medical termination of pregnancy.

If a pregnancy occurs despite an intra-uterine device in situ, the device must be removed before administration of [RH056 trade name].

Medical termination of developing intra-uterine pregnancy with [RH056 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 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 [RH056 trade name] may be required, depending on the clinical situation.

Bleeding

The patient must be informed of prolonged vaginal bleeding (an average of about 9 days or more after administration of [RH056 trade name]) which may be heavy. Bleeding occurs in almost all cases and is not a proof of complete expulsion; persistent bleeding beyond this period may indicate incomplete abortion or an undiagnosed ectopic pregnancy.

Infection

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 symptoms of infection, have been reported after medical abortion with misoprostol tablets. Clinicians should be aware of this potentially fatal complication.

Any reproductive tract infections should be treated before [RH056 trade name] is given.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Misoprostol must not be used during developing pregnancies in which the intent is to proceed, because of a risk of fetal malformation when misoprostol is given during pregnancy.

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 potential abnormalities such as neural tube defects.

Patients considering medical termination of pregnancy should be counselled on the risks to the fetus if termination with [RH056 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.

Breast-feeding

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 and the risk to the infant is therefore minimal after a single dose. In practical terms, breast-feeding can be continued.

Fertility

Adverse effects on male or female fertility or reproduction occurred in rats at doses much higher than the maximum recommended human dose.

Adverse effects on fertility in humans have not been seen. Women may become pregnant again soon after termination of pregnancy with misoprostol. Where appropriate, the woman should start contraception immediately after succesful 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.

Misoprostol may cause dizziness and tiredness. Patients should be instructed that if they have 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
Common	vomiting, diarrhea
Skin and subcutaneous tissue disorders	
Uncommon	Rash
Rare	urticaria, erythroderma, erythema nodosum, toxic epidermal necrolysis
Very rare	Angioedema
Musculoskeletal and connective tissue disorders	
Not known	back pain
Congenital, familial, and genetic disorders	
Common	fetal malformations
Rare	fetal death

General disorders and administration site disorders

Very common	shivering, fever (including temperatures ≥40°)
Common	Chills
Uncommon	Fatigue

When used for *induction of labour*, uterine hyperstimulation and rupture as well as fetal distress may also occur.

When used for *abortion* the following adverse events were also reported:

- uterine cramping,
- prolonged menstrual-like bleeding, on average for nine days (up to 45 days),
- incomplete abortion.
- genital tract infection and uterine rupture (both rarely).

Women should be advised to return for follow-up if they are experiencing prolonged heavy bleeding or fever.

Rare but serious cardiovascular accidents (myocardial infarction and/or spasm of the coronary arteries and severe hypotension) have been reported after use of misoprostol.

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

Symptoms linked to overdose of misoprostol include fever, vascular disorders, nausea, diarrhoea, abdominal cramping and tremors. There is no known antidote for misoprostol overdose. In an overdose, the patient should be closely monitored and symptoms managed as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other gynaecologicals, prostaglandins.

ATC code: G02AD06

Misoprostol is a synthetic analogue of alprostadil (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, a prostaglandin analogue such as misoprostol when used after mifepristone increases the success rate to about 95 percent of the cases and accelerates the expulsion of the conceptus.

Systematic review has also found that use misoprostol following treatment with letrozole results in lower rates of ongoing pregnancy and higher rates of successful abortion than misoprostol alone. In addition, fewer women experience side-effects, based on moderate-certainty evidence. The suggested combination regimen of letrozole plus misoprostol may be safe and effective up to 14 weeks of gestation but further evidence is

needed to determine the safety, effectiveness and acceptability of the combination at later gestational ages, especially in comparison with mifepristone plus misoprostol.

5.2 Pharmacokinetic properties

Absorption of [RH056 trade name]
The absorption characteristics of [RH056 trade name] have been determined after administration of a single dose tablet in healthy volunteers under fed condition as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**
Maximum concentration (C_{max})	419 ± 142 pg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	1075 ± 318 pg.h/mL
Time to attain maximum concentration (tmax)	2.00 ± 0.87h

Pharmacokinetics of 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 compared to the oral route.
Absorption	
Absolute bioavailability	NA
Oral bioavailability	Approximately 7% (as misoprostol acid)
Food effect	↓ Cmax, ↔ AUC (oral administration)
Distribution	
Volume of distribution	Approximately 14 L/kg (active metabolite)
Plasma protein binding *in vitro*	< 90% misoprostol, 85% active metabolite
Tissue distribution	NA
Metabolism	
	de-esterification. Misoprostol acid is further metabolised by beta oxidation on the alpha side chain, omega oxidation of the beta-side chain and reduction to prostaglandin F analogues.
Elimination	
Elimination half-life	13–40 minutes (active metabolite)
Mean systemic clearance (Cl/F)	Approximately 0.29 L/kg/minute (active metabolite)
% of dose excreted in urine	73%
% of dose excreted in faeces	15%
Special populations	
Renal impairment	No dose changes are required for any degree of renal impairment
Hepatic impairment	Severe hepatic impairment may alter pharmacokinetics.

5.3 Preclinical safety data

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

Hydrogenated castor oil

Hypromellose (HPMC)

Microcrystalline cellulose

Sodium starch glycolate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30 °C. Store tablets in blisters in the provided cartons.

6.5 Nature and contents of container

The tablets are packed in cold form aluminium (Alu-Alu) blister packs of 10 tablets. Each carton contains 10 such blisters packs. Pack size: 10x10 Tablets.

The tablets were packed in cold form aluminium (Alu-Alu) blister of 3 tablets one such blister packed in monocarton and Each outer carton contains 10 such monocarton of 1 blister each. Pack size: 10x1x3 Tablets.

The tablets were packed in cold form aluminium (Alu-Alu) blister of 4 tablets one such blister packed in monocarton and Each outer carton contains 10 such monocarton of 1 blister each. Pack size: 10x1x4 Tablets.

The tablets were packed in cold form aluminium (Alu-Alu) blister of 4 tablets one such blister packed in monocarton and Each outer carton contains 15 such monocarton of 1 blister each. Pack size: 15x1x4 Tablets.

The tablets were packed in cold form aluminium blister of 10 tablets. Each carton contains 6 such blister. Pack size: 6x10 Tablets.

6.6 Special precautions for disposal and other handling

Extemporaneous oral formulation

For misoprostol doses of 25 µg for induction of labour, 1 tablet of [RH056 trade name] should be dispersed in 200 mL of water and 25 mL of that mixture, equivalent to 25 µg misoprostol, should be given for each single oral dose.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH056

9. DATE OF PREQUALIFICATION

27 April 2016

10. DATE OF REVISION OF THE TEXT

November 2022
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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines