# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Misoprostol 200 µg Tablets[1]

## 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

Misoprostol 200µg Tablets is indicated for prevention of postpartum haemorrhage when oxytocin is not available.

Misoprostol 200µg Tablets is indicated for induction of labour at term and for termination of pregnancy with a fetal anomaly or after intrauterine fetal death in the third trimester of pregnancy.

Misoprostol is not recommended for induction of labour in women with a scarred uterus (e.g. due to previous caesarean section).

Misoprostol 200µg Tablets in combination with mifepristone is indicated for spontaneous and induced abortion.

It is also used for incomplete abortion.
It should be prescribed and administered in accordance with countries' national laws and regulations.

The most recent official guidelines should be taken into consideration for deciding on the appropriateness of therapy with misoprostol. Official guidance will normally include WHO and public health authorities guidelines (see sections 4.4 and 5.1, and web links in reference section at end of this document).

## 4.2 Posology and method of administration

*Posology*

Prevention of postpartum hemorrhage (PPH)

In settings where oxytocin is unavailable, a single dose of oral misoprostol 600 µg may be used.

Method of administration
To ensure administration of the full dose tablets should be swallowed whole and not be broken or crushed.

Induction of labour and termination of pregnancy with a fetal anomaly or after intrauterine fetal death in the third trimester
25 µg misoprostol, 2-hourly, until start of labour.
If labour has not ensued when the 8$^{th}$ dose (200µg misoprostol in total) has been administered, the patient should be re-evaluated.

Method of administration
For induction of labour one misoprostol 200µg tablet should be dissolved in 200 ml of water and 25 ml of that solution, equivalent to 25µg misoprostol, should be administered as a single dose.

Spontaneous and Induced Abortion

The medication(s) should be administered under the supervision of a healthcare provider able to assess the gestational age of an embryo and to diagnose ectopic pregnancies (see section 4.3). The healthcare provider must also be able to ensure surgical intervention in cases of incomplete abortion or severe bleeding, and provide blood transfusion and resuscitation if necessary.

Incomplete abortion with a gestational age of 13 weeks or less

600µg, as a single dose.

*Please see section 4.3 for specific contraindications in abortion setting*

Treatment for medical abortion less than 7 weeks (49 days) of pregnancy

First, mifepristone 200 mg orally is given.
Then, 24 to 48 hours later: Misoprostol 400 µg, as a single dose.

For further information the Summary of Product Characteristics of mifepristone-containing products should also be consulted.

Method of administration

To ensure administration of the full dose the tablets should be swallowed whole and not be broken or crushed.

*Food effect*

Concomitant ingestion of food decreases the bioavailability of oral misoprostol. Therefore, misoprostol should preferably be administered in the fasted state. However, it can be given without consideration of food intake if needed in life-threatening situations.

*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).

*Paediatric population*

Limited data are available for women under 18 years.

## 4.3 Contraindications

- Hypersensitivity to misoprostol or to any of the excipients listed in section 6.1
- Known allergy to prostaglandins

*Contraindications in abortion setting:*

The following conditions are contraindications for misoprostol in abortion: • Previous allergic reaction to one of the drugs involved

- Inherited porphyria
- Chronic or acute adrenal or hepatic failure
- Known or suspected ectopic pregnancy (neither misoprostol nor mifepristone will induce abortion in ectopic pregnancy)

## 4.4 Special warnings and precautions for use

Caution is warranted in women with pre-existing heart disease or cardiovascular risk factors, as cardiovascular events have been reported in association with misoprostol.

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

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

When misoprostol is used for abortion women should be advised to return for follow-up if they are experiencing signs of ongoing pregnancy.

Misoprostol 200µg Tablets should not be used in children below pubertal age.

This medicinal product contains hydrogenated castor oil. This may cause stomach upset and diarrhoea.

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

Interaction studies showed that the pharmacokinetics of propranolol and diazepam are not influenced by

concomitant administration of misoprostol.

Misoprostol does not change the pharmacokinetics of antipyrine, suggesting that it does not induce hepatic enzymes.

In a pivotal study performed with misoprostol, no adverse events which would suggest the existence of an interaction between misoprostol and oxytocin were reported in women exposed to prophylactic oxytocin (intramuscular or intravenous) prior to 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.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*
Misoprostol must not be used during intact pregnancy in which the intent is to proceed, as a risk of fetal malformation cannot be excluded when misoprostol is administered during pregnancy.

In a few cases where misoprostol was self-administered (orally or vaginally) during pregnancy, the following deleterious effects have been observed: malformations of limbs, abnormal foetus movements and cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements).

Animal studies have not demonstrated teratogenicity but have shown fetotoxicity at high doses.
Available data regarding 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 woman wishes to continue it. Women should, nevertheless, be informed that due to the unknown risk to the fetus of abortifacient drugs, follow-up is important.

*Breast-feeding*
The levels of misoprostol in breast milk are low and decline very rapidly: after 5 hours of 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 were observed in rats at doses much higher than the maximum recommended human dose. Adverse effects on fertility or reproduction in humans appear unlikely.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Headache, dizziness and tiredness have been reported during treatment with misoprostol. Patients 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

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 shortlived.

Tabulated list of adverse reactions
Safety of another misoprostol formulation has been evaluated in 1428 women treated for post-partum haemorrhage.

The adverse reactions reported in the clinical program are provided in the table below and are classified according to frequency and system organ class. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Undesirable effects are ranked under headings of frequency. Within each frequency grouping, the adverse reactions are presented in order of decreasing seriousness.

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).

| **MeDRA System Organ Class** | **Adverse reactions (frequency)** | | | |
|---|---|---|---|---|
| | **Very Common** | **Common** | **Uncommon** | **Rare** |
| **Nervous System Disorders** | | Headache<br>Fainting/Dizziness | | |
| **Gastrointestinal Disorders** | Nausea | Vomiting/Diarrhea | | |
| **Skin and subcutaneous tissue disorders** | | | | Allergic reaction |
| **General disorders and administration site disorders** | Shivering<br>Fever, including temperature ≥40 degrees C. | Chills | Fatigue | |

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

When used for abortion the following adverse events were reported in addition:
Uterine cramping, prolonged menstrual-like bleeding, on average for nine days (up to 45 days), incomplete abortion. Rarely, genital tract infection and uterine rupture.
Women should be advised to return for follow-up if they are experiencing prolonged heavy bleeding or fever.

**Reporting of suspected adverse reactions**

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. Healthcare professionals are asked to report any suspected adverse reactions via https://pv.pharmacyboardkenya.org

## 4.9 Overdose

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

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 fibers in the myometrium.

## 5.2 Pharmacokinetic properties

*Absorption:*
When administered orally, misoprostol, an ester, is rapidly and completely de-esterified to pharmacologically active carboxylic acid in the stomach.
No detectable concentrations of the parent ester can be found in plasma, and only approximately 7% of the dose is systematically bioavailable as the acid after oral administration.

Following single dose oral administration of one misoprostol 200µg tablet in healthy volunteers, mean (SD) misoprostolic acid $C_{max}$ was 442 (173) pg/ml and the mean (SD) $AUC_{0-t}$ was 985 (316) pg.h/ml. Peak plasma concentrations ($T_{max}$) were observed at 1.63 (1.01) hours.

Concomitant ingestion of food decreases the bioavailability of oral misoprostol.

No pharmacokinetic or other data are available for this product for other routes or methods of administration than those described in section 4.2.

*Distribution*
In both young and elderly subjects, misoprostol acid is 85% bound to serum albumin plasma protein in a concentration-independent fashion. Serum protein binding is reduced in the presence of high salicylic acid concentrations (>100 mcg/ml). It has not

been reported whether relative proportions of the stereoisomers in systemic circulation are the same as of different proportions in the tablet.

*Metabolism*
Misoprostol acid is further metabolized by beta oxidation on the alpha side chain, omega oxidation of the

beta-side chain and reduction to prostaglandin F analogs.

*Elimination*
Misoprostolic acid has a plasma half-life of 13-40 minutes.
Approximately 80% of radioactivity is recovered in urine after an oral dose of 3H-misoprostol. A negligible amount of the parent compound or misoprostolic acid appears in urine.

*Renal impairment*
Plasma concentrations of misoprostol acid were measured 4 hours after administration of a single dose of misoprostol 400 µg in 20 patients with various degrees of renal impairment and in 10 healthy subjects. No statistically significant differences in mean plasma concentration were observed among groups of patients with renal impairment. Moreover, there was no correlation between AUC and rate of clearance of 51CrEDTA. Values for $C_{max}$, AUC, $t_{1/2}$ of misoprostol acid for all patients with renal impairment were significantly higher than those in the 10 healthy subjects, possibly reflecting changes in the volume of distribution or other disease-related factors. These differences however do not require modification of misoprostol dosage.

*Hepatic impairment*
Patients with severe hepatic dysfunctions may exhibit altered misoprostol pharmacokinetics.
However, in patients with mild hepatic disease and because of significant interpatient variability in misoprostol acid pharmacokinetics, it is difficult to make definitive recommendations.

## 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.

### 6.6 Special precautions for disposal

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

## 7. SUPPLIER

ACME Formulation Pvt. Ltd.
Ropar Road, Nalagarh, Dist. Solan
Himachal Pardesh-174101
India

## 8. WHO REFERENCE NUMBER (PREQUALIFICATION NUMBER)

RH 056

## 9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF PREQUALIFICATION

27 April 2016

## 10. DATE OF REVISION OF THE TEXT

February 2017