SUMMARY OF PRODUCT CHARACTERISTICS

TABLE OF CONTENTS

1. NAME OF MEDICINAL PRODUCT

- **Brand Name** : MISO-FEM
- **Generic Name** : Misoprostol Tablets 200 mcg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Label Claim:

Each uncoated tablet contains:
Misoprostol……200 mcg
Excipients.....q.s.

Qualitative-Quantitative formula:

S. No.	Ingredients	Qty / Tablet (in mg)	% Qty / Tablet	Function	y Reference
Blending					
1.	Misoprostol HPMC 1% Dispersion[1]	20.00	10.00	API	USP
2.	Microcrystalline Cellulose (Avicel PH113)	20.00	10.00	Diluent	Ph. Eur.
3.	Microcrystalline Cellulose (Avicel PH112)[2]	156.00	78.00	Diluent	Ph. Eur.
4.	Sodium Starch Glycolate	3.00	1.50	Disintegrant	Ph. Eur.
Lubrication					
5.	Castor Oil, Hydrogenated	1.00	0.50	Lubricant	Ph. Eur.
Total Weight of Tablet		**200.00**	**100.00**	**N/A**	**N/A**

N/A: Not Applicable; Ph. Eur.: European Pharmacopoeia

[1] Quantity to be calculated based on actual assay on dried / anhydrous basis as per respective COA.

[2] Quantity of Microcrystalline cellulose (Avicel PH112) to be calculated based on the actual quantity of Misoprostol to maintain a constant theoretical tablet weight.

3. PHARMACEUTICAL FORM

White to off-white, round, bevel edged, flat faced tablets with "J" debossed above and "08" below the score line on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Prevention of postpartum hemorrhage
- Treatment of postpartum haemorrhages
- Treatment of incomplete abortion and missed miscarriage in the first trimester
- Cervical ripening
- Induction of labour (living and dead foetus).

4.2 Posology and method of Administration

Prevention of postpartum hemorrhage:
600 mcg orally administered immediately after the delivery of the baby and confirmation that all foetuses have been delivered (in case of multiple births).

Treatment of postpartum haemorrhage: 800mcg sublingually or l000mcg administered rectally, significantly reduces the need for additional interventions.

Treatment of incomplete abortion and missed miscarriage in the first trimester: 800mcg administered vaginally or sublingually and repeated after 24hours.

(Healthcare provider is advised to offer all women receiving medical management of miscarriage, pain relief, antibiotics and anti-emetics as needed.)

Cervical ripening: For cervical priming prior to transcervical procedure; 400mcg vaginally or orally 3 hours before the procedure.

Induction of labour (living or dead foetus):

For living foetus: 25mcg intravaginally stat, then repeat every 3-6 hours up to 6 doses maximum. (Not to be used in patients with caesarean delivery or major uterine surgery).

For intrauterine foetal death (IUFD): of 13-17 weeks- 200mcg vaginally every 6 to 12 hours for a total of 4doses. lUFD from 18-26weeks: 100mcgvaginallyevery6-12 hours for a total of 4 doses.

IUFD beyond 26 weeks: for unripe cervix (Bishop score<6), vaginal misoprostol 25-S0mcg every 4 hours-up to 6 doses; if cervix is ripe (Bishop score>6), use a first dose of 25-S0mcg and subsequent doses should be doubled to 50-l00mcg if the contractions are not effective.

Maximum daily dosing is 600mcg. Repeat after 24 hours if expulsion has not occurred.

4.3 Contraindications

Misoprostol is contraindicated:

• In women who are pregnant, or in whom pregnancy has not been excluded, or who are planning a pregnancy as misoprostol increases uterine tone and contractions in pregnancy which may cause partial or complete expulsion of the products of conception. Use in pregnancy has been associated with birth defects.

• In patients with a known hypersensitivity to misoprostol or to any other component of the product, or to other prostaglandins.

4.4 Special Warnings and Precautions for Use

Women of childbearing potential should not be started on misoprostol until pregnancy is excluded and should be fully counselled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, use of the product should be discontinued.

In such patients it is advised that MISO-FEM should only be used if the patient:

• takes effective contraceptive measures
• has been advised of the risks of taking MISO-FEM if pregnant (see Contraindications)

Gastrointestinal bleeding, ulceration, and perforation have occurred in NSAID-treated patients receiving misoprostol. Physicians and patients should remain alert for ulceration, even in the absence of gastrointestinal symptoms, and, where appropriate, endoscopy and biopsy should be carried out before use to ensure that malignant disease is absent in the upper gastrointestinal tract. These investigations and any others considered necessary by the clinician should be repeated at appropriate intervals for follow-up purposes.

Symptomatic responses to misoprostol do not preclude the presence of gastric malignancy.

Misoprostol should be used with caution in patients with conditions that predispose them to diarrhoea, such as inflammatory bowel disease. To minimise the risk of diarrhoea,

misoprostol should be taken with food, and magnesium-containing antacids should be avoided.

Misoprostol should be used with caution in patients in whom dehydration would be dangerous. These patients should be monitored carefully.

The results of clinical studies indicate that Misoprostol does not produce hypotension at dosages effective in promoting the healing of gastric and duodenal ulcers. Nevertheless, Misoprostol should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g. cerebrovascular disease, coronary artery disease or severe peripheral vascular disease including hypertension.

There is no evidence that Misoprostol has adverse effects on glucose metabolism in human volunteers or patients with diabetes mellitus.

4.5 Interaction with other medicaments and other forms of interaction

Concomitant administration of NSAIDs and misoprostol in rare cases can cause a transaminase increase and peripheral oedema.

MISO-FEM is predominantly metabolised via fatty acid oxidising systems and has shown no adverse effect on the hepatic microsomal mixed function oxidase (P450) enzyme system. In specific studies no clinically significant pharmacokinetic interaction has been demonstrated with antipyrine or diazepam. A modest increase in propranolol concentrations (mean approximately 20% in AUC, 30% in Cmax) has been observed with multiple dosing of misoprostol. In extensive clinical studies no drug interactions have been attributed to Misoprostol. Drug interaction studies with misoprostol and several NSAIDs showed no clinically significant effect on the kinetics of ibuprofen, diclofenac, piroxicam, aspirin, naproxen or indomethacin.

Magnesium-containing antacids should be avoided during treatment with misoprostol as this may worsen the misoprostol-induced diarrhoea.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Misoprostol is contraindicated in women who are pregnant because it induces uterine contractions and is associated with abortion, premature birth, foetal death and birth defects.

First trimester exposure to misoprostol is associated with a significantly increased risk of two birth defects: Möbius sequence (i.e. palsies of cranial nerves VI and VII) and terminal transverse limb defects. Other defects including arthrogryposis have been observed.

The risk of uterine rupture increases with advancing gestational age and with prior uterine surgery, including Caesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

Lactation

Misoprostol is rapidly metabolized in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. Misoprostol should not be administered to nursing mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhoea in nursing infants.

4.7 Effects on ability to drive and use machines

MISO-FEM can cause dizziness. Patients should be cautioned about operating machinery and driving.

4.8 Undesirable Effects

The adverse reaction terms were then categorized utilizing the incidence rate as follows:

Immune System Disorder
Not Known: Anaphylactic reaction

Nervous System Disorders
Common: Headache, Dizziness

Gastrointestinal Disorders
Very common: Diarrhoea*
Common: Abdominal pain*, constipation, dyspepsia, flatulence, nausea, vomiting

Skin and Subcutaneous Tissue Disorders
Very Common: Rash

Pregnancy, Puerperium, and Perinatal Conditions
Not Known: Amniotic fluid embolism, abnormal uterine contractions, foetal death, incomplete abortion, premature birth, retained placenta, uterine rupture, uterine perforation.

Reproductive System and Breast Disorders
Uncommon: Vaginal haemorrhage (including postmenopausal bleeding), intermenstrual bleeding, menstrual disorder, uterine cramping.
Rare: Menorrhagia, dysmenorrhoea
Not Known: Uterine haemorrhage

Congenital, Familial and Genetic Disorders
Not Known: Birth defects

General Disorders and Administration Site Conditions

Not Known: Chills
Uncommon: Pyrexia

** Diarrhoea and abdominal pain were dose-related, usually developed early in the course of therapy, and were typically self-limiting. Rare instances of profound diarrhoea leading to severe dehydration has been reported.*

4.9 Overdose

Signs and Symptoms of Overdose

The toxic dose of misoprostol in humans has not been determined. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhoea, fever, palpitations, hypotension, or bradycardia.

Treatment of Overdose

Because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage. In cases of overdose, standard supportive measures should be adopted as required.

In clinical trials patients have tolerated 1200 micrograms daily for three months without significant adverse effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

MISO-FEM is an analogue of naturally occurring prostaglandin E_1 which promotes peptic ulcer healing and symptomatic relief.
MISO-FEM protects the gastro duodenal mucosa by inhibiting basal, stimulated and nocturnal acid secretion and by reducing the volume of gastric secretions, the proteolytic activity of the gastric fluid, and increasing bicarbonate and mucus secretion.

5.2 Pharmacokinetic Properties

MISO-FEM is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite (misoprostol acid) occurring after about 30 minutes. The plasma elimination half-life of misoprostol acid is 20-40 minutes. No accumulation of misoprostol acid in plasma occurs after repeated dosing of 400 micrograms twice daily.

5.3 Preclinical Safety Data

In single and repeat-dose studies in dogs, rats and mice at multiples of the human dose, toxicological findings were consistent with the known pharmacological effects of the E-type prostaglandins, the main symptoms being diarrhoea, vomiting, mydriasis, tremors and hyperpyrexia. Gastric mucosal hyperplasia was also observed in the mouse, rat and the dog.

In the rat and the dog the hyperplasia was reversible on discontinuation of misoprostol following one year of dosing. Histological examination of gastric biopsies in humans has shown no adverse tissue response after up to one year's treatment. In studies of fertility, teratogenicity and peri/post-natal toxicity in rats and rabbits there were no major findings. A decrease in implantations and some pup growth retardation was observed at doses greater than 100 times the human dose. It was concluded that misoprostol does not significantly affect fertility, is not teratogenic or embryotoxic and does not affect rat pups in the peri/post-natal period.

Misoprostol was negative in a battery of 6 in vitro assays and one in vivo test to assess mutagenic potential. In carcinogenicity studies in the rat and mouse it was concluded that there was no risk of carcinogenic hazard.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose (Avicel PH112)
Microcrystalline Cellulose (Avicel PH113)
Sodium Starch Glycolate (Type A)
Hydrogenated Castor Oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special Precaution for Storage

Store below 30°C, away from direct light. Keep out of reach of children.

6.5 Nature and contents of container

One or three Aluminium /Aluminium blister pack containing 4 tablets along with pack insert in a carton.

6.6 Special precautions for disposal and other handling

No Special Requirements.

7. MARKETING AUTHORISATION HOLDER

NAARI Pte, Singapore.

8. MARKETING AUTHORISATION NUMBER(S)

Not Applicable.

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Not Applicable.

10. DATE OF REVISION OF THE TEXT

Not Applicable