1. Name of the medicinal product

MISOPROSTOL TABLETS 200 MCG

2. Qualitative and quantitative composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIAL SPECIFICATION	LABLE CLAIM	OVERAGES %	QTY. / TABLET	PURPOSE
ACTIVE INGREDIENTS						
1.	Misoprostol (1% HPMC dispersion)	USP	200.00 mcg	0.00 %	20.000 mg	API
INACTIVE INGREDIENTS						
2.	Maize starch	BP	-	0.00 %	86.000 mg	Diluent
3.	Microcrystalline cellulose	BP	-	0.00 %	86.000 mg	Diluent
4.	Magnesium stearate	BP	-	0.00 %	2.000 mg	Lubricant
5.	Purified talc	BP	-	0.00 %	4.000 mg	Glidant
6.	Colloidal silicon dioxide	USP	-	0.00 %	2.000 mg	Glidant

3. Pharmaceutical form

Oral Tablet

4. Clinical particulars

4.1 Therapeutic indications

Misoprostol Tablets 200 mcg is indicated for the healing of duodenal ulcer and gastric ulcer including those induced by nonsteroidal anti-inflammatory drugs (NSAID) in arthritic patients at risk, whilst continuing their NSAID therapy. In addition, Misoprostol Tablets 200 mcg can be used for the prophylaxis of NSAID-induced ulcers.

4.2 Posology and method of administration

Adults
Healing of duodenal ulcer, gastric ulcer and NSAID-induced peptic ulcer: 800 micrograms daily in two or four divided doses taken with breakfast and / or each main meal and at bedtime.
Treatment should be given initially for at least 4 weeks even if symptomatic relief has been achieved sooner. In most patients ulcers will be healed in 4 weeks but treatment may be continued for up to 8 weeks if required. If the ulcer relapses further treatment courses may be given.
Prophylaxis of NSAID-induced peptic ulcer: 200 micrograms twice daily, three times daily or four times daily. Treatment can be continued as required. Dosage should be individualised according to the clinical condition of each patient.
Elderly
The usual dosage may be used.

Renal impairment: Available evidence indicates that no adjustment of dosage is necessary in patients with renal impairment.
Hepatic impairment: Misoprostol Tablets 200 mcg is metabolised by fatty acid oxidising systems present in organs throughout the body. Its metabolism and plasma levels are therefore unlikely to be affected markedly in patients with hepatic impairment.
Children
Use of Misoprostol Tablets 200 mcg in children has not yet been evaluated in the treatment of peptic ulceration or NSAID-induced peptic ulcer disease.

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 counseled 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 Misoprostol Tablets 200 mcg should only be used if the patient:
- Takes effective contraceptive measures
- Has been advised of the risks of taking Misoprostol Tablets 200 mcg if pregnant

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 Tablets 200 mcg does not produce hypotension at dosages effective in promoting the healing of gastric and duodenal ulcers. Nevertheless, Misoprostol Tablets 200 mcg 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 Tablets 200 mcg has adverse effects on glucose metabolism in human volunteers or patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of NSAIDs and misoprostol in rare cases can cause a transaminase increase and peripheral oedema.
Misoprostol Tablets 200 mcg 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 Tablets 200 mcg. 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 metabolised 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

Misoprostol Tablets 200 mcg 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: Anaphylactic reaction
Nervous System Disorders: Dizziness, headache
Gastrointestinal Disorders: Diarrhoea**,** Abdominal pain, constipation, dyspepsia, flatulence, nausea, vomiting
Skin and Subcutaneous Tissue Disorders: Rash
Pregnancy, puerperium, and perinatal conditions: Amniotic fluid embolism, abnormal uterine contractions, foetal death, incomplete abortion, premature birth, retained placenta, uterine rupture, uterine perforation.
Reproductive System and Breast Disorders: Vaginal haemorrhage (including postmenopausal bleeding), intermenstrual bleeding, menstrual disorder, uterine
Rare: Cramping, Menorrhagia, dysmenorrhea, Uterine haemorrhage
Congenital, Familial and Genetic Disorders: Birth defects
General Disorders and Administration Site Conditions: Chills, Pyrexia

The pattern of adverse events associated with Misoprostol Tablets 200 mcg is similar when an NSAID is given concomitantly.

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

Misoprostol Tablets 200 mcg is an analogue of naturally occurring prostaglandin E1 which promotes peptic ulcer healing and symptomatic relief.
Misoprostol Tablets 200 mcg protects the gastroduodenal 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

Misoprostol Tablets 200 mcg 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

- Maize starch
- Microcrystalline cellulose
- Magnesium stearate
- Purified talc
- Colloidal silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store in a dry place at a temperature below 30°C.

6.5 Nature and Contents of Container

10 X 10 Tablets Alu-Alu pack, packed in printed and laminated carton.

6.6 Special Precautions for Disposal and Other Handling

No Special Requirements

7. Marketing Authorisation Holder

West Coast Pharmaceutical Works LTD., Ahmedabad

8. Marketing Authorisation Number(s)

Not applicable

9. Date of First Authorisation/Renewal of the Authorisation

Not applicable

10. Date of Revision of the Text

July, 2018