

## SUMMARY OF PRODUCT CHARACTERISTICS

### MISOPROSTOL TABLETS 200MCG

1. **NAME OF DRUG PRODUCT:** Misoprostol 200mcg Tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITIONS:**

Each film coated tablet contains:

Misoprostol 200mcg

Name of components	Specifications	Quantity per mg	Function
Misoprostol	IH	0.22	Active
Microcrystalline Cellulose	BP	26.67	Diluent
Maize Starch	BP	88.67	Diluent & Binder
Lactose	BP	77.67	Binder
Methyl Hydroxybenzoate	BP	0.2	Preservative
Propyl Hydroxybenzoate	BP	0.04	Preservative
Povidone	BP	3.33	Binder
Isopropyl Alcohol	BP	Q,S	Solvent
Purified Talc	BP	2.5	Lubricant
Magnesium Stearate	BP	3.67	Lubricant
Colloidal Anhydrous Silica	BP	1.33	Glidant
Sodium Starch Glycolate	BP	3.67	Disintegrant
<b>Coating Material</b>			
Unique coat FC	IH	5	Film forming agent
Purified Talc	BP	1.33	Lubricant
Isopropyl Alcohol	BP	Q,S	Solvent
Dichloromethane	BP	Q,S	Solvent
Titanium dioxide	BP	0.833	Coloring agent

3. **PHARMACEUTICAL FORM**

Film coated tablets

4. **Clinical particulars**

4.1 **Therapeutic indications**

Misoprostol Tablets 200mcg 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 200mcg can be used for the prophylaxis of NSAID-induced ulcers.

#### **4.2 Posology and method of administration**

##### **Posology:**

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.

**Renal impairment:** Available evidence indicates that no adjustment of dosage is necessary in patients with renal impairment.

**Hepatic impairment:** Misoprostol Tablets 200mcg 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.

Elderly

The usual dosage may be used.

Paediatric population

Use of Misoprostol Tablets 200mcg in children has not yet been evaluated in the treatment of peptic ulceration or NSAID-induced peptic ulcer disease.

**Method of administration:** Oral

#### **4.3 Contraindications**

Misoprostol is contraindicated:

- In women of childbearing potential who are not using effective contraception (see sections 4.4, 4.6 and 4.8)
- 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 (see sections 4.4, 4.6 and 4.8). 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**

In women of childbearing potential Misoprostol Tablets 200mcg must 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 (see sections 4.3, 4.6 and 4.8).

In such patients it is advised that Misoprostol Tablets 200mcg should only be used if the patient:

- takes effective contraceptive measures
- has been advised of the risks of taking Misoprostol Tablets 200mcg if pregnant (see section 4.3)

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 (see section 4.5).

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 200mcg does not produce hypotension at dosages effective in promoting the healing of gastric and duodenal ulcers. Nevertheless, Misoprostol Tablets 200mcg 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 200mcg 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 200mcg 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  $C_{max}$ ) has been observed with multiple dosing of misoprostol. In extensive clinical studies no drug interactions have been attributed to Misoprostol Tablets 200mcg. 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**

##### Women of childbearing potential

Women of childbearing potential must be informed about the risk of teratogenicity prior to treatment with Misoprostol Tablets 200mcg. Treatment must not be initiated until pregnancy is excluded, and women should be fully counselled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, treatment must be immediately discontinued (see sections 4.3 and 4.4).

##### Pregnancy

##### Misoprostol

Misoprostol induces uterine contractions and is associated with abortion, premature birth, foetal death and foetal malformations.

Approximately a 3-fold increased risk of malformations was reported in pregnancies exposed to misoprostol during the first trimester, compared to a control group incidence of 2%. In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of suckling and deglutition and eye movements, with or without limb defects); amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, oligodactyly, cleft palate inter alia) and central nervous system anomalies (cerebral and cranial anomalies as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects). Other defects including arthrogyposis have been observed.

Consequently:

- Women should be informed of the risk of teratogenicity.
- Should the patient wish to continue with her pregnancy after exposure of misoprostol in utero, a careful ultrasound scan monitoring of the pregnancy, with special attention to the limbs and head must be carried out.

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.

##### Breast-feeding

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 200mcg can cause dizziness. Patients should be cautioned about operating machinery and driving..

#### 4.8 Undesirable effects

The Adverse reaction terms were then categorised utilising the incidence rate as follows:

Very Common: $\geq 1/10$ ( $\geq 10\%$ )	
Common: $\geq 1/100$ and $< 1/10$ , ( $\geq 1\%$ and $< 10\%$ )	
Uncommon: $\geq 1/1000$ and $< 1/100$ , ( $\geq 0.1\%$ and $< 1\%$ )	
Rare: $\geq 1/10,000$ and $< 1/1000$ , ( $\geq 0.01\%$ and $< 0.1\%$ )	
Very Rare: $< 1/10,000$ , ( $< 0.01\%$ )	
Not Known	
Immune System Disorder Not Known	Anaphylactic reaction
Nervous System Disorders Common	Dizziness, headache
Gastrointestinal Disorders Very common Common	Diarrhoea* Abdominal pain*, constipation, dyspepsia, flatulence, nausea, vomiting
Skin and Subcutaneous Tissue Disorders Very Common	Rash
Pregnancy, puerperium, and perinatal conditions Rare Not Known	Uterine rupture** Amniotic fluid embolism, abnormal uterine contractions, foetal death, incomplete abortion, premature birth, retained placenta, uterine perforation
Reproductive System and Breast Disorders Uncommon  Rare Not Known	Vaginal haemorrhage (including postmenopausal bleeding), intermenstrual bleeding, menstrual disorder, uterine cramping Menorrhagia, dysmenorrhoea Uterine haemorrhage
Congenital, Familial and Genetic Disorders Common	Foetal malformations
General Disorders and Administration Site Conditions Not Known Uncommon	Chills 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.

\*\*Uterine rupture has been uncommonly reported after prostaglandin intake during the second or third trimester of pregnancy. Uterine ruptures occurred particularly in multiparous women or in women with a caesarean section scar.

Diarrhoea can be minimised by using single doses not exceeding 200 micrograms with food and by avoiding the use of predominantly magnesium containing antacids when an antacid is required.

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

#### Clinical trials:

In clinical trials, over 15,000 patients and subjects received at least one dose of misoprostol. Adverse reactions involved primarily the gastrointestinal system.

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The profile for adverse reactions with >1% incidence was similar for subacute (four to twelve weeks duration) and long- term (up to one year) clinical trials.

The safety of long-term (greater than 12 weeks) administration of misoprostol has been demonstrated in several studies in which patients were treated continuously for up to one year. This includes no adverse or unusual change in the morphology of gastric mucosa, as determined by gastric biopsy.

#### Special populations:

There were no significant differences in the safety profile of misoprostol in patients who were 65 years of age or older, compared with younger patients.

The use of misoprostol in children has not been evaluated.

### **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**

Pharmacotherapeutic group: prostaglandins, ATC code: A02BB01.

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

#### Mechanism of action

Misoprostol Tablets 200mcg 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 200mcg 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

Maize Starch

Lactose

Methyl Hydroxybenzoate  
Propyl Hydroxybenzoate  
Povidone  
Isopropyl Alcohol  
Purified Talc  
Magnesium Stearate  
Colloidal Anhydrous Silica  
Sodium Starch Glycolate  
Unique coat FC  
Purified Talc  
Isopropyl Alcohol  
Dichloromethane  
Titanium dioxide

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

24 months.

**6.4 Special precautions for storage**

Store below 30<sup>0</sup>C.

**6.5 Nature and contents of container**

10 tablets are placed in a ALU-PVC blister; 1 Such Alu-Pvc blisters are packed in a unit carton along with package insert.

**6.6 Special precautions for disposal and other handling**

Protect from light.

**7. MARKETING AUTHORIZATION HOLDER:**

PROTECH BIOSYSTEMS PVT LTD

**8. MANUFACTURING AUTHORIZATION HOLDER:**

PROTECH BIOSYSTEMS PVT LTD

**9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION:**

**10. DATE OF REVISION OF THE TEXT**