Summary of Product Characteristics

MISOBRIL

(Misoprostol 200 microgram Tablets)

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1 Name of the medicinal product

MISOBRIL – Misoprostol 200 microgram Tablets

2 Qualitative and quantitative composition

Each uncoated tablet contains misoprostol BP 200 micrograms.

Excipient(s) with known effect
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3 Pharmaceutical form

Uncoated tablet.

White, hexagonal, uncoated tablets with a break-line on one side and plain on the other side.

4 Clinical particulars

4.1 Therapeutic indications

MISOBRIL is indicated for the healing of duodenal ulcer and gastric ulcer, including those induced by non-steroidal anti-inflammatory drugs (NSAIDs) in arthritic patients at risk, whilst continuing their NSAID therapy. In addition, MISOBRIL 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. The 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 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 in children has not yet been evaluated in the treatment of peptic ulceration or NSAID-induced peptic ulcer disease.

Method of administration
For oral administration. To minimise the risk of diarrhoea, MISOBRIL should be taken with food (see section 4.4).

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, to any other component of the product, or to other prostaglandins.

4.4 Special warnings and precautions for use

Women of childbearing potential
In women of childbearing potential, MISOBRIL must not be started until pregnancy is excluded, and the patient 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 MISOBRIL should only be used if the patient:

- takes effective contraceptive measures;
- has been advised of the risks of taking MISOBRIL if pregnant (see section 4.3).

The patient should not give MISOBRIL to anyone else. It is prescribed for a patient's specific condition, may not be the correct treatment for another person, and may be dangerous to that person, particularly if she were to become pregnant.

Gastrointestinal effects
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.

Diarrhoea and dehydration
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.

Cardiovascular disorders
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, MISOBRIL should be used with caution in the presence of disease states where hypotension might precipitate severe complications, for example cerebrovascular disease, coronary artery disease or severe peripheral vascular disease including hypertension.

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

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Misoprostol 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 and 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 indometacin.

Magnesium-containing antacids should be avoided during treatment with misoprostol, as this may worsen 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 MISOBRIL. 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 is contraindicated in women who are pregnant. 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 with a control group incidence of 2%. In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, difficulties with suckling and deglutition, and abnormal eye movements, with or without limb defects); amniotic band syndrome (limb deformities and amputations, especially clubfoot, acheiria, oligodactyly and cleft palate, among others); and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly,

cerebellar hypoplasia and neural tube defects). Other defects, including arthrogryposis, have been observed.

Consequently:

- women should be informed of the risk of teratogenicity;
- should the patient wish to continue with her pregnancy after exposure to misoprostol in utero, 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.

Fertility

In studies of fertility in rats and rabbits there were no major findings, and it was concluded that misoprostol does not significantly affect fertility (see section 5.3). No clinical data on the effect of misoprostol on human fertility are available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions are listed below by System Organ Class and frequency. Frequencies are defined as: 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) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Not known	Anaphylactic reaction
Nervous system disorders	Common	Dizziness, headache
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	Rare	Uterine rupture**
	Not known	Amniotic fluid embolism, abnormal uterine contractions, foetal death, incomplete abortion, premature birth, retained placenta, 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	Common	Foetal malformations
General disorders and administration site conditions	Uncommon	Pyrexia

System Organ Class	Frequency	Adverse reaction
	Not known	Chills

* 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 have 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.

Description of selected adverse reactions

Diarrhoea can be minimised by using single doses not exceeding 200 micrograms taken 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 is similar when an NSAID is given concomitantly.

In clinical trials, over 15,000 patients and subjects received at least one dose of misoprostol. Adverse reactions involved primarily the gastrointestinal system. The profile for adverse reactions with an incidence greater than 1% was similar for subacute (four to twelve weeks' duration) and long-term (up to one year) clinical trials. The safety of long-term administration (greater than 12 weeks) 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 the 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.

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 to the National Regulatory Authority.

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, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension or bradycardia.

Treatment of overdose

Because misoprostol is metabolised 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 1,200 micrograms daily for three months without significant adverse effects.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for peptic ulcer and gastro-oesophageal reflux disease; prostaglandins.

ATC code: A02BB01

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

Mechanism of action
Misoprostol protects the gastroduodenal mucosa by inhibiting basal, stimulated and nocturnal acid secretion, and by reducing the volume of gastric secretions and the proteolytic activity of the gastric fluid, while increasing bicarbonate and mucus secretion.

Pharmacodynamic effects
Misoprostol inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli including meals, histamine and pentagastrin. Activity is apparent approximately 30 minutes after oral administration and persists for at least 3 hours. Misoprostol also produces uterine contractions, which is the basis of its contraindication in pregnancy (see sections 4.3 and 4.6).

5.2 Pharmacokinetic properties

Absorption
Misoprostol is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite (misoprostol acid) occurring after about 30 minutes. Administration with food reduces the rate, but not the overall extent, of absorption of misoprostol acid.

Distribution and biotransformation
Misoprostol undergoes rapid de-esterification to its free acid, misoprostol acid, which is responsible for the clinical activity and, unlike the parent compound, is detectable in plasma. Misoprostol acid is less than 90% bound to plasma proteins, and this binding is concentration-independent over the therapeutic range.

Elimination
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. Misoprostol is metabolised by fatty acid oxidising systems present in organs throughout the body, and the metabolites are excreted principally in the urine.

5.3 Preclinical safety data

In single-dose 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 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
- Sodium starch glycolate
- Hypromellose
- Hydrogenated castor oil
- Isopropyl alcohol
- Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

ALU-PVC blisters of 10 tablets. Five blisters are packed in a carton together with a package insert (50 tablets per carton).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 Marketing authorisation holder

National Pharmacy Limited

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Nairobi

Kenya

8 Marketing authorisation number

CTD12268

9 Date of first authorisation/renewal of the authorisation

23.07.2026

10 Date of revision of the text

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