EPROSTOL 200MCG TABLETS

1. Name of the medicinal product
Eprostol 200 microgram tablets

2. Qualitative and quantitative composition
Each tablet contains 200 micrograms misoprostol.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablet

White to off-white hexagonal tablets scored both sides, engraved SEARLE 1461 on one side for oral administration.

4. Clinical particulars
4.1 Therapeutic indications
Eprostol 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, Eprostol 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: Eprostol 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 Eprostol 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 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 Eprostol 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 Eprostol should only be used if the patient:

• takes effective contraceptive measures

• has been advised of the risks of taking Eprostol 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 Eprostol does not produce hypotension at dosages effective in promoting the healing of gastric and duodenal ulcers. Nevertheless, Eprostol 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 Eprostol has adverse effects on glucose metabolism in human volunteers or patients with diabetes mellitus.

Excipient information

Eprostol 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 in rare cases can cause a transaminase increase and peripheral oedema.

Eprostol 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 Eprostol. *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 Eprostol. 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, olygodactyly, cleft palate inter alia) and central nervous system anomalies (cerebral and cranial anomalies as anencephaly, hydrocephaly, cerebellar hypoplasia, 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 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
Eprostol 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: ≥ 1/10 (≥ 10%)	
Common: ≥ 1/100 and < 1/10, (≥ 1% and <10%)	
Uncommon: ≥ 1/1000 and < 1/100, (≥ 0.1% and <1%)	
Rare: ≥ 1/10,000 and < 1/1000, (≥ 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 Eprostol 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.

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.

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.

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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.

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

Mechanism of action

Eprostol 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

Eprostol 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

Sodium starch glycolate (Type A)

Hydrogenated castor oil

Hypromellose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30° C. Store in the original package to protect from moisture.

6.5 Nature and contents of container
Cold-formed aluminium blister packs of 56, 60, 112, 120 or 140 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

Zolon Healthcare Limited,Located at No 11 Town planning way Ilupeju, Lagos

8. Marketing authorisation number(s)

NA

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: NA

NA

10. Date of revision of the text

NA