Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Misonext Tablet 200 mcg (Misoprostol USP)

2. Qualitative and quantitative composition
Misonext Tablet 200 mcg
Each film coated tablet contains Misoprostol USP 200 mcg
See list of excipients 6.1

3. Pharmaceutical form
Oral Solid Tablet
Misonext Tablet 200 **mcg** is a white to off white colored, round shape, uncoated flat beveled edged tablet with one side cross breakline and other side plain

4. Clinical particulars

4.1 Therapeutic indications
Misonext 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, Misonext 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: Misonext 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 Misonext 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 Misonext 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 Misonext should only be used if the patient:

• takes effective contraceptive measures

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

Excipient information

Misonext 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.

Misonext 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 Misonext. 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 Pregnancy and Lactation

Women of childbearing potential

Women of childbearing potential must be informed about the risk of teratogenicity prior to treatment with Misonext. 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

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

4.8 Undesirable effects

Misoprostol is an E1 prostaglandin analogue and so, in contrast to other prostaglandins, it has no significant effect on the lungs or blood vessels (and so can be used in asthmatics). With doses over 400mcg, diarrhea can occur and some patients experience a brief increase in temperature with shivering. Both effects are dose dependent and settle rapidly without treatment. Patients can experience shivering and pyrexia (usually no more than 38-39°C). If needed administer antipyretics such as paracetamol.

The most frequent gastrointestinal adverse events are diarrhea (13% of all patients) and abdominal pain (7%). Diarrhea is dose related and usually develops early and is self-limiting. Rare instances of profound diarrhea, leading to severe dehydration have been reported. Patients with an underlying condition, such as inflammatory bowel disease, or those in whom dehydration would be dangerous should be monitored carefully if Misonext is prescribed. The incidence of diarrhea could be minimized if administering after meals or at bedtime, and by avoiding co-administration of Misonext with predominantly magnesium containing antacids.

The following gynecological disorders have been reported: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%), and dysmenorrhoea (0.1%). Postmenopausal vaginal bleeding may be related to Misonext administration. If it occurs diagnostic workup should be undertaken to rule out gynecological pathology. There are no significant differences in the safety profile patients using Misonext for prevention and treatment of ulcers who are 65 years of age or older compared with younger patients. The following adverse reactions were reported by more than 1% of the patients receiving Misonext and may be casually related to the drug: nausea (3.2%), flatulence (2.9%, headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). Mild shivering and pyrexia have been reported when Misonext has been used for postpartum hemorrhage. These symptoms are transient and typically resolve without intervention. Other rare symptoms are nausea, vomiting, headache, diarrhea, and possibility of skin rashes.

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 pharmacy and poisons board Pharmacovigilance Electronic Reporting System PvERS https://pv.pharmacyboardkenya.org.

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.

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

Mechanism of action

Misonext 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

Misonext 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 (Type 102)
- Crospovidone
- Sodium Starch Glycolate
- Hydrogenated Castor oil

6.2 Incompatibilities

Not applicable**.**

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Store at temperature not exceeding 30°C in a dry place. Protect from light & moisture**.**

6.5 Nature and Content of container

Misonext tablet 200 mcg: each box contains 3x10's tablets in Alu-Alu blister pack

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

HEALTHCARE PHARMACEUTICAL S LIMITED,

8. Marketing Authorization Number

CTD10844

9. Date of first authorization/renewal of the authorization

FEB 16, 2024.

10. Date of revision of the text

MAY 14, 2025.