1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

ACEMISO 200 mcg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

ACEMISO: Each tablet contains 200 micrograms misoprostol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

ACEMISO: white to off white, round, biconvex, uncoated tablets, plain on both sides

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ACEMISO is indicated for co-administration with non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of gastric and duodenal ulcers, haemorrhagic lesions and erosions induced by NSAIDs.

4.2 Posology and method of administration

Posology

For the prevention of gastric ulcers, haemorrhagic lesions and erosions induced by NSAIDs:

A minimum of 200 mcg (one tablet) with food twice daily, together with the prescribed NSAID. Dosage may be increased to 200 mcg three times daily or to a maximum of 200 mcg four times daily, to correspond to the NSAID administration schedule or if indicated by the clinical condition of the patient.

For the prevention of duodenal ulcers induced by NSAIDs:

800 mcg (four tablets) daily in divided doses, with food.

Antacids containing aluminium may be given as needed for relief of pain.

Special populations

Elderly

The usual dosage may be used.

Paediatric population

Safety and effectiveness in children under the age of 18 years have not been established.

Method of administration

For oral use

To minimise the risk of diarrhoea, ACEMISO should be taken with food, and magnesium containing antacids should be avoided.

4.3 Contraindications

Misoprostol is contraindicated:

Hypersensitivity to misoprostol, other prostaglandins or to any of the excipients of **ACEMISO** listed in section 6.1.

• 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 moderate to severe impaired renal function.

4.4 Special warnings and precautions for use

ACEMISO should not be used in pregnant women as teratogenicity in animals have been demonstrated and it induces uterine contractions and therefore has abortifacient potential.

In women of childbearing potential **ACEMISO** must not be started until pregnancy is excluded and should be fully counselled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, use **ACEMISO** should be discontinued (see sections 4.3, 4.6 and 4.8).

In such patients it is advised that **ACEMISO** should only be used if the patient:

• takes effective contraceptive measures

• has been advised of the risks of taking **ACEMISO** if pregnant (see section 4.3)

Gastrointestinal bleeding, ulceration, and perforation have occurred in NSAID-treated patients receiving misoprostol.

Medical practitioners 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.

ACEMISO 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 **ACEMISO** has adverse effects on glucose metabolism in human volunteers or patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

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

ACEMISO is predominantly metabolised via fatty acid oxidising systems and has shown no adverse effect on the hepatic microsomal mixed function oxidase (P450) enzyme system.

A modest increase in propranolol concentrations (mean approximately 20% in AUC, 30% in C_{max}) has been observed with multiple dosing of misoprostol.

Medicine 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

<u>Women of childbearing potential</u>

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

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

ACEMISO is contraindicated during pregnancy (see section 4.3)

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

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

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

The table below lists the adverse reactions observed during use of misoprostol.

Immune System Disorder Frequency unknown	Anaphylactic reaction
Nervous System Disorders Frequent	Dizziness, headache
Gastrointestinal Disorders Frequent	Diarrhoea* Abdominal pain*, constipation, dyspepsia, flatulence, nausea, vomiting
Skin and Subcutaneous Tissue Disorders Frequent	Rash

Pregnancy, puerperium, and perinatal conditions Less frequent Frequency unknown	 Uterine rupture** Amniotic fluid embolism, abnormal uterine contractions, foetal death, incomplete abortion, premature birth, retained placenta, uterine perforation
Reproductive System and Breast Disorders Less frequent Frequency unknown	 Vaginal haemorrhage (including postmenopausal bleeding), intermenstrual bleeding, menstrual disorder, uterine cramping Menorrhagia, dysmenorrhoea Uterine haemorrhage
Congenital, Familial and Genetic Disorders Frequent	 Foetal malformations
General Disorders and Administration Site Conditions Frequency unknown Less frequent	 Chills Pyrexia

Description of selected adverse reactions

* 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 **ACEMISO** is similar when an NSAID is given concomitantly.

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 SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: prostaglandins, ATC code: A02BB01.

Pharmacological classification: A11.10 Medicines acting on the gastrointestinal tract.

Pharmacological action:

Misoprostol is a synthetic prostaglandin E, analogue which has gastric antisecretory and mucosal protective properties. The antisecretory activity is mediated by direct action on specific prostaglandin receptors on the surface of gastric parietal cells. The mucosal protective effect against various damaging agents has been demonstrated in humans with doses that inhibit, and doses which minimally affect acid secretion.

Antisecretory activity:

Effect on acid secretion: In healthy human subjects, misoprostol inhibits daytime and nocturnal basal gastric acid secretion and acid secretion stimulated by histamine, pentagastrin, food, tetragastrin, betazole and coffee.

Effect on pepsin secretion and gastric fluid volume: Misoprostol decreases pepsin and gastric volume under basal conditions.

Effect on serum gastrin: Misoprostol has no persistent effects on fasting levels of, or on postprandial increase in, serum gastrin.

Mucosal protective activity:

Misoprostol has properties in animals and humans that strengthen the integrity of the gastroduodenal mucosal barrier against damaging agents. These include stimulation of duodenal bicarbonate secretion and gastric mucus production. In addition, misoprostol maintains mucosa! haemodynamics.

Other pharmacological effects:

Misoprostol has been shown to produce uterine contractions which may endanger pregnancy (see section 4.3).

Misoprostol does not produce clinically significant effects on serum prolactin, gonadotrophins, TSH, GH, thyroxine, cortisol, gastro-intestinal hormones (somatostatin, gastrin, vaso-active intestinal polypeptide and motilin), creatinine, or uric acid, gastric emptying, immunological competence, platelet aggregation, pulmonary function, or the cardiovascular system.

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. 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.

Distribution

The free acid of misoprostol is less than 90 % bound to plasma proteins. Misoprostol is metabolised by fatty acids-oxidising systems, present in several organs of the human body.

Elimination

After oral administration of 3H-misoprostol approximately 73 % of the radioactivity is excreted in urine and approximately 15 % in the faeces. Approximately 56 % of total radioactivity is eliminated within 8 hours via urine.

Administration of misoprostol with food does not change the bioavailability of misoprostol acid, but reduces the maximum plasma concentration due to a slower absorption rate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose

sodium starch glycolate

hydrogenated castor oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25°C.

Store in the original package in order to protect from moisture. Keep out of reach of children.

6.5 Nature and contents of container

ACEMISO is packed in cold form ALU-ALU blister packs in cartons of 56, 60, 112 or 120 or 140 tablets**.**

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

96 Hartley Road

Durban, 4091

8 REGISTRATION NUMBER(S)

55/11.10/0503

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT