SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

CYTOTEC® Tablets

COMPOSITION:

Each tablet contains 200 mcg misoprostol.

The inactive ingredients include; microcrystalline cellulose, sodium starch glycolate and hydrogenated castor oil.

PHARMACOLOGICAL CLASSIFICATION:

A 11.10 Medicines acting on the gastro-intestinal tract - Special combinations and/or substances.

PHARMACOLOGICAL ACTION:

Misoprostol is a synthetic prostaglandin E_1 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 mucosal haemodynamics.

Other pharmacological effects:

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

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.

Pharmacokinetic properties:

Misoprostol is rapidly absorbed following oral administration. After an oral dose of radiolabelled misoprostol, about 73 % of the administered radio-activity is excreted in the urine. Pharmacokinetic studies in patients with mild to moderate renal impairment showed an increase in $T_{½}$, C_{max} and AUC in renal impaired, compared to normal patients. In patients with total renal failure, there was an approximate two-fold increase in AUC in four of six patients. Misoprostol does not accumulate in red blood cells.

The serum protein binding of misoprostol acid is less than 90 % and is concentration-independent in the therapeutic range. Misoprostol is metabolised by fatty-acid oxidising systems (beta and omega oxidation) which are present in organs throughout the body. Its

metabolism and plasma levels are therefore unlikely to be markedly affected in hepatically-impaired patients. Misoprostol does not interfere with hepatic medicine-metabolising enzymes nor hepatic blood flow in animals. In multiple-dose human studies, misoprostol did not alter the pharmacokinetics or the bio-availability of propranolol, antipyrine or diazepam.

Misoprostol bio-availability was reduced (by 16 %) when it was co-administered with high doses of antacid. Administration of misoprostol with a high fat content meal did not alter the extent of misoprostol absorption but did reduce the rate of absorption resulting in lower C_{max} and higher T_{max} values for misoprostol acid.

In healthy elderly subjects over 64 years of age, the AUC for misoprostol acid was slightly increased from that in younger subjects. This was attributed to the reduced clearance probably due partly to decreased volume of distribution and a slight prolongation of elimination $T_{½}$ of this metabolite in the elderly.

INDICATIONS:

CYTOTEC 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.

CONTRAINDICATIONS:

CYTOTEC should not be administered to anyone with a known hypersensitivity to misoprostol or other prostaglandins.

CYTOTEC is contraindicated in patients who are pregnant or in whom pregnancy has not been excluded and in lactation (See Warnings and Special Precautions and Pregnancy and Lactation sections).

Moderate to severely impaired renal function.

WARNINGS and SPECIAL PRECAUTIONS:

CYTOTEC SHOULD NOT BE USED IN PREGNANT WOMEN AS TERATOGENICITY IN ANIMALS HAS BEEN DEMONSTRATED AND IT INDUCES UTERINE CONTRACTIONS AND THEREFORE HAS ABORTIFACIENT POTENTIAL.

WOMEN OF CHILDBEARING POTENTIAL SHOULD NOT BE STARTED ON CYTOTEC UNTIL PREGNANCY IS EXCLUDED AND SHOULD BE FULLY COUNSELLED ON THE IMPORTANCE OF ADEQUATE CONTRACEPTION WHILE UNDERGOING TREATMENT.

Symptomatic responses to CYTOTEC do not preclude the presence of gastric malignancy.

Patients with conditions that predispose to diarrhoea, such as inflammatory bowel disease, or those in whom dehydration would be dangerous, should be monitored carefully.

In animals, prostaglandins of the E type have the capacity to produce hypotension through peripheral vasodilation. The results of clinical trials indicate that CYTOTEC does not produce hypotension at dosages of up to 800 mcg per day. However, CYTOTEC should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g. cerebral vascular disease or coronary artery disease. Gastro-intestinal bleeding, ulceration, and perforation have occurred in NSAID-treated patients receiving CYTOTEC. Physicians and patients should remain alert for ulceration, even in the absence of gastro-intestinal symptoms.

Effects on ability to drive and use machines

The effect of CYTOTEC on the ability to drive or use machinery has not been systematically evaluated.

INTERACTIONS

Interaction studies with CYTOTEC showed no clinically significant effect on the kinetics of ibuprofen, diclofenac, piroxicam or indomethacin. CYTOTEC also did not exert any clinically significant effect on the steady-state blood level or anti-platelet effects of therapeutic doses of aspirin.

PREGNANCY AND LACTATION

CYTOTEC is contraindicated in women who are pregnant because it induces uterine contractions and is associated with abortion, premature birth and foetal death and birth defects. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and excreted in the breast milk.

CYTOTEC should not be administered to breastfeeding mothers because the potential excretion of misoprostol acid could cause diarrhoea in nursing infants.

DOSAGE AND DIRECTIONS FOR USE

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.

To minimize the risk of diarrhoea, CYTOTEC should be taken with food, and magnesium-containing antacids should be avoided.

No dosage adjustment is recommended in older patients.

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

SIDE EFFECTS

The following adverse events have been reported in association with CYTOTEC therapy. In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100<1/10), uncommon (≥ 1/1,000, <1/100) and rare (<1/1,000)).

System Organ Class	Frequency	Adverse Reaction
Nervous System Disorders	Common	Dizziness, headache
Gastrointestinal Disorders	Very Common	Diarrhoea*
	Common	Abdominal pain*,constipation, dyspepsia, flatulence, nausea, vomiting
Reproductive System and Breast Disorders	Uncommon	Vaginal haemorrhage(including postmenopausal bleeding, menstrual disorder, uterine cramping
	Rare	Menorrhagia, dysmenorrhoea
*The diarrhoea, abdominal pain are transient and mild in severity, self limiting and require discontinuation of CYTOTEC in the minority of patients. Instances of profound diarrhoea leading to severe dehydration have been reported. Dose adjustment may also be helpful.		

Post – marketing Experience

Reactions from post-marketing experience include the following:

Immune system: Anaphylactic reaction

Skin and Subcutaneous tissue:rash

Pregnancy, puerperium and perinatal conditions: abnormal uterine contractions, amniotic fluid embolism, foetal death, incomplete abortion, premature birth, retained placenta, uterine perforation, uterine rupture.

Reproductive System and Breast Disorder: Uterine haemorrhage.

Congenital Familial and Genetic Disorder: Birth defects.

General Disorder and Administration Site Condition: chills, pyrexia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension and bradycardia. Symptoms should be treated with supportive therapy. Because CYTOTEC is metabolised like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

IDENTIFICATION:

CYTOTEC tablets are white, scored, uncoated, flat, hexagonal-shaped tablets, debossed on one side “SEARLE” over “1461”.

PRESENTATION:

CYTOTEC tablets are supplied in blister packs of 60 or 120 tablets packed in cartons.

STORAGE INSTRUCTIONS:

Store in the original packaging in a dry place at or below 30 ºC.

Do not use after expiration date. Keep out of reach of children.

REGISTRATION NUMBER:

S/11.10/392

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd.

85 Bute Lane

Sandton 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

25 November 2011

NAMIBIA: S2
Reg No.: 90/11.10/001301

BOTSWANA: S2
Reg No.: B9311470

ZIMBABWE: PP
Reg No.: 99/16.7/3507

ZAMBIA:
Reg No.: 120/037