Pfizer
Cytotec ®
Misoprostol
Reference Market-CDS
Nigeria, Ghana

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cytotec 200 mcg 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

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

Misoprostol is indicated for:

- The coadministration with nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment and prevention of gastric and duodenal ulcers, hemorrhagic lesions and erosions induced by NSAIDs.
- The treatment of active duodenal and gastric ulcers.
- The treatment of erosive gastroduodenitis associated with peptic ulcer disease.

4.2 Posology and method of administration

Use in the prevention of ulcers, erosions, and hemorrhagic lesions in patients maintained on NSAID therapy

The recommended total daily dose is 400 micrograms to 800 micrograms per day in two to four divided doses. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate, misoprostol tablets should be taken simultaneously with NSAIDs. Misoprostol should be taken for the duration of NSAID therapy.

Use in the treatment of gastric and duodenal ulcers, including those associated with NSAID use; and treatment of erosive gastritis associated with peptic ulcer disease

The recommended total daily dose is 800 micrograms per day in two to four divided doses for a minimum of four weeks.

Use in Women of Childbearing Potential, (**see Section 4.3 –Contraindications, Section 4.4 - Special warnings and precautions for use and 4.6 –Pregnancy and lactation**)

Use in Renal Impairment

Dosage may need to be reduced in patients with renal failure, (**See section 5.2 Pharmacokinetic properties, *Impaired Renal Function).***

Use in the Elderly

No dosage adjustment is recommended in older patients.

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

4.3 Contraindications

Misoprostol is contraindicated in patients:
- Who are pregnant, or in whom pregnancy has not been excluded, (**see Section 4.4 – Special warnings and precautions for use, Section 4.6 Pregnancy and Lactation, and Section 4.8 Undesirable Effects, POST-MARKETING SURVEILLANCE).**

- With a known hypersensitivity to misoprostol or any other component of the product, or to other prostaglandins.

4.4 Special warnings and precautions for use

-Women of childbearing potential should not be started on misoprostol until pregnancy is excluded, and should be fully counseled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, use of the product should be discontinued, (**see Section 4.3 Contraindications, Section 4.6 –Pregnancy and Lactation and Section 4.8 Undesirable Effects, POST-MARKETING SURVEILLANCE**).

- 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.

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

- Patients with conditions that predispose them to diarrhea, such as inflammatory bowel disease. To minimize the risk of diarrhea, misoprostol should be taken with food, and magnesium-containing antacids should be avoided.

- Patients in whom dehydration would be dangerous-. These patients should be monitored carefully.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interaction studies with misoprostol and several NSAIDs showed no clinically significant effect on the kinetics of ibuprofen, diclofenac, piroxicam, aspirin, naproxen or indomethacin. Misoprostol does not interfere with the beneficial effects of NSAIDs on the signs and symptoms of rheumatoid arthritis and osteoarthritis.

4.6 Pregnancy and lactation

Pregnancy
Misoprostol is contraindicated in women who are pregnant because it induces uterine contractions and is associated with abortion, premature birth , and fetal death and birth defects. (**See section 4.3 Contraindications, Section 4.4 – Special warnings and precautions for use and Section 4.8 Undesirable Effects, POST-MARKETING SAFETY SURVEILLANCE).**

Lactation

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 diarrhea in nursing infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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. Adverse reactions with incidences > 1% included the following:

Nervous System Disorders: dizziness, headache
Gastrointestinal Disorders: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, vomiting

Diarrhea and abdominal pain were dose-related, usually developed early in the course of therapy, and were typically self-limiting. Rare instances of profound diarrhea 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:

Adverse reactions all occurring with incidences < 1% in women during clinical trials included the following:

Reproductive System and Breast Disorders: dysmenorrhea, intermenstrual bleeding menorrhagia, menstrual disorder, uterine cramping, vaginal hemorrhage (including postmenopausal bleeding

There were no significant differences in the safety profile of misoprostol in patients whowere 65 years of age or older, compared with younger patients.

The following adverse events were reported during POST-MARKETING SURVEILLANCE:

Immune System Disorder: Anaphylactic reaction

Skin and Subcutaneous Tissue Disorders: rash

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

Reproductive System and Breast Disorders: uterine hemorrhage.

Congenital, Familial and Genetic Disorders: birth defects.

General Disorders and Administration Site Conditions: chills, pyrexia.

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, diarrhea, 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

Misoprostol is a synthetic prostaglandin E_1 analog with ulcer healing, gastric acid antisecretory and mucosal protective properties. The antisecretory activity is mediated by direct action on specific prostaglandin receptors on the surface of gastric parietal cells.

In healthy human subjects, misoprostol inhibits daytime and nocturnal basal gastric acid secretion and acid secretion stimulated by histamine, pentagastrin, food, tegagastrin, betazole, and coffee. This antisecretory effect is apparent 30 minutes after administration and persists for at least three hours. In general, only the 200 mcg dose had substantial effects on nocturnal secretion or on histamine and meal-stimulated secretion.

Misoprostol decreases pepsin output, gastric acid output and gastric fluid volume under basal conditions, and under some stimulated conditions.

Misoprostol stimulates duodenal bicarbonate secretion and gastric mucous production. In addition, misoprostol maintains mucosal hemodynamics.

Misoprostol has been shown to produce uterine contractions that may terminate pregnancy.

5.2 Pharmacokinetic properties

Absorption: In healthy volunteers, misoprostol is rapidly absorbed after oral administration with a Tmax of misoprostol acid of 12 ± 3 minutes. Mean peak plasma concentrations (C_{max}) after single doses show a linear relationship vs. dose over the dose range of 200 to 400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days.

Distribution: The serum protein binding of misoprostol acid is < 90% and is concentration-independent in the therapeutic range.

Metabolism: Misoprostol is rapidly and extensively metabolized to the free acid, which is the principal pharmacologically active metabolite in the blood.

Excretion: Misoprostol is eliminated rapidly with a terminal half-life ($t_{1/2}$) of about 20-30 minutes. After oral administration of radiolabeled misoprostol, about 73% of the administered radioactivity is excreted in urine primarily as inactive polar metabolites.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid.

Misoprostol does not affect the cytochrome P-450 enzyme system in animals.

Specific patient populations:

Impaired renal function: Pharmacokinetic studies in patients with mild to moderate renal impairment showed an increase in $t_{1/2}$ C_{max}, and AUC in renally impaired patients compared to normals. No clear correlation was found between the degree of renal impairment and AUC. In patients with total renal failure, there was an approximate two-fold increase in AUC in four of six patients, (**See section 4.2 Posology and method of administration, Use in Renal Impairment**).

5.3 Preclinical safety data

The mutagenic/carcinogenic potential of misoprostol was tested in seven *in vitro* tests and in one *in vivo* test, all of which were negative.

There was no evidence of an effect of misoprostol on tumor occurrence or incidence in rats or in mice.

There was no evidence of teratogenicity in rabbits at dosages up to 1000 mcg/kg nor in rats at dosages up to 10,000 mcg/kg, which were the highest dosages feasible to test because of maternal toxicity. Rabbits given 1000 mcg/kg had an increased incidence of embryonic deaths. Rats given 1,600 mcg/kg had decreased implantations compared to a control group, but the values remained within the historical control range for the strain. Post-implantation embryonic/fetal loss was observed in rats given 10,000 mcg/kg.

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

Keep out of the sight and reach of children.

Do not use cytotec after the expiry date which is stated on the carton /blister after EXP: The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Store below 30°C. Store in the original package.

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. FURTHER INFORMATION

MANUFACTURED BY

Piramal Healthcare UK Limited
Whalton Road, Morpeth
United Kingdom

8. PRESCRIPTION STATUS

Prescription Only Medicine (POM)

9. DATE OF REVISION OF THE TEXT

September 2017