**CYTOTEC 200 mcg TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Cytotec 200mcg tablets.

## 2. QUALITATIVE & QUANTITATIVE COMPOSITION

Each tablet contains 200 micrograms misoprostol.

For excipients, see 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

- For the treatment of duodenal and gastric ulcer.

Treatment and prevention of NSAID induced ulcers lesions, erosions, while NSAID therapy continues.

- Use in conjunction with Mifepristone subject to the approval of a committee for the termination of pregnancy according to the Israeli penal law 1977.

- Failure of pregnancy in the first trimester

The usage is designated to empty the uterus in a state of failure in the first trimester including pregnancy: when a pregnancy sac was presented in the uterus with no foetus eco, rejected abortion (until week 11+6 and a foetus length of 40 mm) or incomplete abortion. The medicine is to be used after the location of the sac in the uterus was proven and the diagnosis of pregnancy failure is assured.

- The usage of the product for this goal is in ambulatory setting. The dosage and route of administration will be similar to the usage of Cytotec in pregnancy termination after the use of Mefigyine. Informed consent and medical monitoring are required .

- Softening and widening of the cervix for intra-uterine procedures

The usage is designed to soften and widen the cervix to perform intra-uterine procedures such as: abortion, hysteroscopy, insertion of IUD and others, according to clinical decision.
The product should be used for this purpose in ambulatory setting .

The route of administration (vaginal,sublingual, buccal, oral or rectal) and the dosage is under the decision of the physician.

## 4.2 **Posology and Method of Administration**

**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. 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. Treatment can be continued as required. Dosage should be individualised according to the clinical condition of each patient.

Use in Women of Childbearing Potential (see Section 4.1 – Therapeutic indications, Section 4.3 – Contraindications, Section 4.4 -Special warnings and precautions for use and 4.6 –Pregnancy and lactation)

**Elderly**

The usual dosage may be used.

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

**Hepatic impairment:** Cytotec 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.

**Children**

Use of Cytotec in children under the age of 18 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 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. With the exception of cases when it is used in combined treatment with mifepristone for termination of pregnancy - subject to approval from an abortion committee. According to Penal law 1997.

- 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 Special Precautions for Use**

Women of childbearing potential should 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).
Cytotec should not be used in pre-menopausal women unless the patient requires nonsteroidal anti-inflammatory (NSAID) therapy and is at high risk of complications from NSAID-induced ulceration.

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

- takes effective contraceptive measures

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

## 4.5 Interactions with other medicaments and other forms of interaction

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

Cytotec 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 Cytotec. 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

Pregnancy

Misoprostol is contraindicated in women who are pregnant because it induces uterine contractions and is associated with abortion, premature birth, foetal death and birth defects. First trimester exposure to misoprostol is associated with a significantly increased risk of two birth defects: Möbius sequence (i.e. palsies of cranial nerves VI and VII) and terminal transverse limb defects. Other defects including arthrogryposis have been observed.

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.

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 diarrhoea in nursing infants.

## 4.7 Effects on ability to drive and to use machines

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

## 4.8 **Undesirable effects**

The Adverse reaction terms were then categorized utilizing the incidence rate as follows:

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|---|
| 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<br>Not Known | <br>Anaphylactic reaction |
| Nervous System Disorders<br>Common | <br>Dizziness, headache |
| Gastrointestinal Disorders<br>Very common<br>Common | <br>Diarrhoea*<br>Abdominal pain*, constipation, dyspepsia, flatulence, nausea, vomiting |
| Skin and Subcutaneous Tissue Disorders<br>Very Common | <br>Rash |
| Pregnancy, puerperium, and perinatal conditions<br>Not Known | <br>Amniotic fluid embolism, abnormal uterine contractions, foetal death, incomplete abortion, premature birth, retained placenta, uterine rupture, uterine perforation |
| Reproductive System and Breast Disorders<br>Uncommon<br><br><br>Rare<br>Not Known | <br>Vaginal haemorrhage (including postmenopausal bleeding), intermenstrual bleeding, menstrual disorder<br>uterine cramping<br>Menorrhagia, dysmenorrhoea<br>Uterine haemorrhage |
| Congenital, Familial and Genetic Disorders<br>Not Known | <br>Birth defects |
| General Disorders and Administration Site Conditions<br>Not Known<br>Uncommon | <br><br>Chills<br>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.*

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 Cytotec 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 under the age of 18 has not been evaluated.

## 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

Cytotec is an analogue of naturally occurring prostaglandin $E_1$ which promotes peptic ulcer healing and symptomatic relief.

Cytotec 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.

The antisecretory activity is mediated by direct action on specific prostaglandin receptors on the surface of gastric parietal cells. In addition, misoprostol maintains mucosal hemodynamics.
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**

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,
Milled Hydrogenated castor oil flake ,
Hydroxypropyl Methyl Cellulose

## 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.

6.5 **Nature and Contents of a Container**

Cold-formed aluminium blister packs of 20 or 28 tablets.
Not all pack sizes may be marketed.

6.6 **Special Instructions for Use/Handling**

No Special Requirements.

**Manufacturer:** Piramal Healthcare UK limited

## 7. MARKETING AUTHORISATION HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd, 9 Shenkar st, Herzliya