Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cytotec 200 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 micrograms misoprostol.

Excipients with known effect:
Contains hydrogenated castor oil, 1.0mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, flat, hexagonal-shaped tablets, scored on both sides with 'SEARLE' over '1461' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management and prophylaxis of peptic ulcers associated with use of non-steroidal anti-inflammatory drugs. In the short-term management of gastric and duodenal ulcer.

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

Elderly
The usual dosage may be used.

Renal impairment: Available evidence indicates that no adjustment of dosage is necessary in patients with renal impairment.

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.

Paediatric population
Use of Cytotec 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 known hypersensitivity to the active substance, misoprostol or to any of the excipients listed in section 6.1 or to other prostaglandins.

4.4 Special warnings and precautions for use

In women of childbearing potential Cytotec 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 of the product should be discontinued (see sections 4.3, 4.6 and 4.8).

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 misoprostol does not produce hypotension at dosages effective in promoting the healing of gastric and duodenal ulcers. Nevertheless, misoprostol 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 Interaction with other medicinal products and other forms of interactions

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

Women of childbearing potential
Women of childbearing potential must be informed about the risk of teratogenicity prior to treatment with Cytotec. 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
Cytotec is contraindicated in women who are pregnant because it 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 misoprostal during the first trimester, compared to a control group incidence of 2%. In particular, prenatal exposure to misoprostal has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking deglutition and eye movements, with or without limb defects); amniotic band syndrome (limb deformities /amputations, especially club foot, 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 misoprostal in utero, a careful ultrasound scan monitoring of the pregnancy, with a 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.

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 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:

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

General Disorders and Administration Site Conditions	
Not Known	Chills
Uncommon	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.*
***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.

Syncope has been infrequently reported.

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.

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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 has not yet been evaluated.

A number of side effects have been reported in clinical studies or in the literature following use of misoprostol for non-approved indications. These include abnormal

uterine contractions, uterine haemorrhage, uterine rupture/perforation, retained placenta, amniotic fluid embolism, incomplete abortion, premature birth, foetal death, and birth defects. (See Section 4.3, Contraindications, Section 4.6, Pregnancy and Lactation and Section and Section 4.4 Special warnings and precautions for use).

Reporting of side effects
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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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. As a PGE_1 analogue it shares some at least, of that hormone's effects on smooth muscle.

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.

5.2 Pharmacokinetic properties

Cytotec 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 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 (Type A)
Hydrogenated castor oil
Hypromellose

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 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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/118/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th April 1989
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10 DATE OF REVISION OF THE TEXT

December 2018