NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Cytotec 200 microgram tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 micrograms misoprostol.

Excipient(s) with known effect

Sodium starch glycollate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Tablet uncoated scored, flat, white, hexagonal, with dimensions 0.830 cm x 0.919cm, debossed on one side with SEARLE 1461.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CYTOTEC is indicated for coadministration with non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of ulcers and erosions induced by NSAIDs in adults.

CYTOTEC is indicated for the treatment of duodenal and gastric ulcers in adults. CYTOTEC is also effective in healing a significant number of duodenal ulcers refractory to H2-blocker therapy.

CYTOTEC is indicated for the treatment of erosive gastroduodenitis associated with peptic ulcer disease in adults.

CYTOTEC is indicated in prevention of stress-induced upper GI mucosal bleeding and lesions in post-surgical adult ICU patients.

4.2 Dose and method of administration

Dose

Duodenal ulcers

800 micrograms per day in two or four divided doses with meals and at bedtime for four to eight weeks.

Gastric ulcers

200 micrograms four times a day with meals and at bedtime for four to twelve weeks.

Prevention of ulcers and erosions in patients continuing NSAID therapy

400 to 800 micrograms a day in divided doses with meals and at bedtime. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate, CYTOTEC and the NSAID should be taken simultaneously.

Gastroduodenitis associated with peptic ulcer disease

800 micrograms per day in divided doses with meals and at bedtime for four to twelve weeks.

Prevention of stress-induced mucosal bleeding and lesions in post-surgical ICU patients

200 micrograms every four hours for up to 14 days.

General

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

Special populations

Elderly

No dosage adjustment is recommended in older patients. Dosage may need to be reduced in patients with renal failure.

Paediatric population

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

4.3 Contraindications

Misoprostol is contraindicated in women who are pregnant, or in patients in whom pregnancy has not been excluded (see sections 4.6 – Pregnancy and 4.8).

Misoprostol should not be administered to anyone with a known hypersensitivity to misoprostol or any other ingredient of the product, or to other prostaglandins.

4.4 Special warnings and precautions for use

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. CYTOTEC is prescribed for a patient's specific condition, it may not be the correct treatment for another person, and may be dangerous to the other person, particularly if she were to become pregnant.

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

Although not observed with CYTOTEC, there is a possibility of nosocomial pulmonary infections associated with bacterial colonisation of the stomach in patients in intensive care units receiving drugs which suppress acid secretion.

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 effective in promoting the healing of gastric and duodenal ulcers. 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.

Epileptic seizures have been reported with prostaglandins and prostaglandin analogues administered by routes other than oral. While there are no reports of epilepsy in patients receiving misoprostol, the possibility should be borne in mind in patients with a history of epilepsy.

Bronchospasm may occur with some prostaglandins and prostaglandin analogues. The possibility should be borne in mind in patients with a history of asthma.

4.5 Interaction with other medicines and other forms of interaction

In clinical trials there was no evidence of interaction between CYTOTEC and cardiac, gastrointestinal, pulmonary, or CNS medicines (see section 5.2). Decreased bioavailability of misoprostol acid was observed with high doses of antacid. However, low doses of antacids administered during ulcer healing trials had no effect on the efficacy of CYTOTEC.

In laboratory studies, misoprostol has no significant effect on the cytochrome P450-linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other medicines normally metabolised by this system.

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 or rheumatoid arthritis and osteoarthritis.

4.6 Fertility, pregnancy and lactation

Fertility

CYTOTEC is not fetotoxic or teratogenic in rats or rabbits at doses 625 times (10,000 micrograms/kg) and 62 times (1000 micrograms/kg) the human dose, respectively. Rabbits given 1000 mcg/kg had an increased incidence of embryonic deaths. In some rat studies with CYTOTEC, there were misoprostol-related decreases in the number of implantation sites at

doses 100 times (1600 micrograms/kg) the human dose but not at doses 63 times the human dose. Post-implantation embryonic/fetal loss was observed in rats given 10,000 mcg/kg.

Pregnancy - Category X

Misoprostol is contraindicated in women who are pregnant because it induces uterine contractions and is associated with abortion, premature birth, and fetal death. Miscarriages caused by misoprostol may be incomplete, which could lead to potentially dangerous bleeding, hospitalisation, surgery, infertility or death. Use of misoprostol has been associated with birth defects (see sections 4.3 and 4.8).

Möbius sequence (i.e. palsies of cranial nerves VI and VII) and terminal transverse limb defects have been associated with first trimester exposure to misoprostol. Other defects including arthrogryposis have been observed. Misoprostol is contraindicated in women who are pregnant (see sections 4.3 and 4.8).

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 (i.e. oral contraceptives or intrauterine devices) while undergoing treatment. Women should be capable of complying with effective contraception and advised not to become pregnant while taking misoprostol. If a woman becomes pregnant while taking misoprostol, use of the product should be discontinued.

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 breastfeeding mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhoea in breastfeeding infants. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the expected benefit of the drug to the mother.

4.7 Effects on ability to drive and use machinery

No data available.

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% were diarrhoea, abdominal pain, nausea, flatulence, dyspepsia, headache, vomiting, constipation, and dizziness.

The profile for adverse reactions with >1% incidence was similar for subacute (four to 12 weeks duration) and long-term (up to one year) clinical trials.

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.

Women who received misoprostol during clinical trials reported the following gynecological disorders: uterine cramping, menorrhagia, menstrual disorder, dysmenorrhoea, intermenstrual bleeding, and vaginal haemorrhage (including postmenopausal bleeding). The incidence of each of these adverse events in women was <1%.There were no significant differences in the safety profile of misoprostol in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

The safety of long term (greater than 12 weeks) administration of misoprostol has been demonstrated in several studies in which subjects 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.

Table 1. Adverse Events According to Incidence

System Organ Class	**Incidence >1%**	**Incidence <1%**
Nervous System Disorders	Dizziness, headache	
Gastrointestinal Disorders	Diarrhoea, abdominal pain, nausea, flatulence, dyspepsia, vomiting and constipation	
Pregnancy, puerperium and perinatal conditions		Uterine cramping, menorrhagia, menstrual disorder, dysmenorrhoea, intermenstrual bleeding and vaginal haemorrhage (including postemenopausal bleeding).

Post-marketing experience

Table 2: Adverse Events Observed in Post-marketing Experience

Immune system disorder	Anaphylactic reaction
Pregnancy, puerperium, and perinatal conditions	Abnormal uterine contractions, uterine rupture/perforation, retained placenta, amniotic fluid embolism, incomplete abortion, premature birth and fetal death have been reported when misoprostol was administered in pregnant women or in patients in whom pregnancy has not been excluded (see sections 4.3 and 4.6)
Reproductive system and breast disorders	Uterine haemorrhage
Congenital, familial and genetic disorders	Birth defects

General disorders and administration site conditions	Chills and pyrexia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

The toxic dose of misoprostol in human beings has not been determined. Cumulative total daily doses of 1600 micrograms have been tolerated with only symptoms of gastrointestinal discomfort being reported.

Clinical signs that may indicate an overdose are: sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension, or bradycardia. Hypertension and tachycardia have also been reported following overdoses. Overdose in pregnancy has resulted in uterine contractions with fetal death.

There is no specific antidote. Treatment should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1 hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Because misoprostol is metabolised like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The chemical name is (+) methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate. The chemical formula of misoprostol is $C_{22}H_{38}O_5$ and the molecular weight is 382.5.

Misoprostol contains approximately equal amounts of two diastereomers, each a racemic mixture of two enantiomers.

Misoprostol is a yellow, viscous liquid with a musty odour.

Mechanism of action

CYTOTEC is a synthetic prostaglandin E_1 analogue which has 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 dogs

with innervated Pavlov pouches, inhibition of secretion is achieved at a lower dosage by intrapouch injection than by intravenous or intragastric administration, suggesting that the local effect may predominate. 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 gastric acid secretion

In the dosage range of 50 microgram to 200 microgram in healthy human subjects, CYTOTEC inhibits gastric acid secretion in the basal state, as well as that stimulated by histamine, pentagastrin, food, tetragastrin, betazole and coffee.

Additionally, CYTOTEC reduces nocturnal basal gastric acid secretion. The duration of inhibition of secretion is observed up to 5 1/2 hours after CYTOTEC administration, while the onset of action is approximately 30 minutes post-dose.

Effect on pepsin secretion and gastric fluid volume

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

Effect on serum gastrin

CYTOTEC has no persistent effects on fasting levels of, or on postprandial increases in serum gastrin.

Effect on intrinsic factor secretion

With pentagastrin as a stimulant, intrinsic factor output is unaffected after 100 micrograms of CYTOTEC.

Mucosal cytoprotective activity

In animals and man, CYTOTEC has mucosal cytoprotective properties that may strengthen the integrity of the gastric mucosal barrier against damaging agents. While the mechanism of mucosal cytoprotection is not fully defined, CYTOTEC stimulates normal physiological mechanisms in the gastroduodenal mucosa. CYTOTEC stimulates bicarbonate secretion in a dose-related manner in the duodenum. It also increases the thickness of adherent mucus in the stomach and the quantity of soluble mucus found in the gastric aspirate. In addition, CYTOTEC 200 microgram increases human mucosal blood volume by more than 15% over baseline. In rats, mucosal blood flow is sustained, whereas, in dogs, it is increased.

Prevention of NSAID induced ulcers

CYTOTEC 200 microgram q.i.d. coadministered with NSAIDs is superior to placebo in preventing NSAID-induced gastric ulcers in osteoarthritis patients. The rate of ulceration was 1.4% with CYTOTEC 200 microgram q.i.d compared with 21.7% with placebo.

In patients with osteoarthritis, CYTOTEC 200 microgram coadministered with aspirin 900 mg q.i.d. reduced faecal blood loss produced by administration of aspirin alone. Pretreatment with

CYTOTEC 25, 50, 100 and 200 microgram reduces aspirin-induced gastric lesions. In addition, 25 and 50 micrograms of CYTOTEC q.i.d. (doses that exert little antisecretory effect) reduce aspirin-induced gastric bleeding and faecal blood loss in healthy human subjects. CYTOTEC 200 microgram q.i.d. completely protected the gastric mucosa against damage induced by 650 mg aspirin q.i.d., whereas no protection was observed with placebo.

Coadministration of CYTOTEC 200 microgram q.i.d. with tolmetin prevented tolmetin-induced gastroduodenal lesions in healthy human subjects.

Similarly, CYTOTEC 200 microgram b.i.d. coadministered with naproxen reduced naproxen-induced lesions.

CYTOTEC 100 microgram or 200 microgram q.i.d coadministered with ibuprofen reduced ibuprofen-induced gastroduodenal lesions.

CYTOTEC has been shown not to affect the course of the arthritis or to interfere with the anti-inflammatory or analgesic properties of the NSAID.

Alcohol

In an ethanol-induced gastritis model in healthy subjects, CYTOTEC 200 micrograms was 80% more protective than placebo.

Prevention of stress lesions and bleeding

Similar efficacy was observed for both 200 microgram misoprostol every four hours and high dose antacid in the prevention of stress ulcers and bleeding in post-surgical patients. However, unlike antacids, treatment with misoprostol did not require aspiration of gastric contents for measurement of pH and subsequent titration of dosage, nor did it induce metabolic alkalosis or produce hypermagnesaemia.

Spontaneous relapse of duodenal ulcer

The 6-month incidence of recurrence of duodenal ulcers after discontinuation of successful healing therapy with CYTOTEC in 202 patients was 44%.

In a separate analysis of spontaneous duodenal ulcer relapse data on patients from 3 multicentre endoscopic trials, the median time to relapse for patients without ulcer history healed on CYTOTEC 200 micrograms q.i.d. was 365 days.

Other Pharmacologic Effects

CYTOTEC has been shown to produce uterine contractions which may endanger pregnancy (see sections 4.3 and 4.6).

CYTOTEC does not adversely affect serum prolactin, gonadotropins, TSH, GH, thyroxine, cortisol, gastrointestinal hormones (somatostatin, gastrin, vasoactive intestinal polypeptide, and motilin), creatinine, or uric acid; gastric emptying, immunologic competence, platelet aggregation, pulmonary function, or the cardiovascular system.

5.2 Pharmacokinetic properties

CYTOTEC is rapidly and extensively metabolised to the free acid, which is the principal pharmacologically active metabolite in the blood. In healthy volunteers, oral absorption of CYTOTEC is rapid. After administration of a single dose, time to peak plasma concentration (t_{max}) for misoprostol acid occurs at 12±3 minutes, and thereafter it is eliminated rapidly with a terminal half-life ($t_{1/2}$) of about 20-30 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. Misoprostol acid undergoes further metabolism by fatty acid oxidizing systems (beta and omega oxidation) which are present in numerous organs throughout the body. Its metabolism and plasma levels are therefore unlikely to be affected markedly in hepatically impaired patients. CYTOTEC does not interfere with the hepatic enzymes which metabolise medicines nor hepatic blood flow in animals.

No accumulation of misoprostol acid in plasma occurs after repeated dosing of 400 micrograms b.i.d; plasma steady state was achieved within two days.

Seventy-three percent of the radioactivity of an oral dose of radio-labelled misoprostol is excreted in the urine primarily as inactive polar metabolites, with an additional 15% excreted in the faeces. About 56% of total radioactivity was eliminated in urine within 8 hours.

The serum protein binding of misoprostol acid, the primary metabolite, is <90% and is concentration-independent in the therapeutic range. There was no accumulation of misoprostol in red blood cells.

With CYTOTEC no relationship was found between the degree of renal insufficiency and the area under the misoprostol acid concentration-time curve (AUC) in 20 patients with Cr-51-EDTA clearance ranging from <0.5 to 36.8 ml/min. Prolongation of mean misoprostol acid $t_{1/2}$ from 26 minutes in healthy subjects to 42 minutes in renally impaired patients was not of sufficient magnitude to require changes in the 200 microgram four-times-a-day dosing schedule in patients. In 4 of 6 anuric patients, there was an approximate two-fold increase in AUC. A starting dose in the low range (e.g. 100 mcg q.i.d) should therefore be considered for patients with total renal failure.

No clinically significant change in the absorption of aspirin, ibuprofen or diclofenac occurred when each of these NSAIDs was given concomitantly with CYTOTEC. CYTOTEC also did not exert any clinically significant effect on the steady-state blood level or antiplatelet effects of therapeutic doses of aspirin.

In multiple dose human studies, CYTOTEC did not alter the pharmacokinetics or the bioavailability of propranolol, antipyrine or diazepam.

CYTOTEC bioavailability was reduced (by 16%) when it was coadministered with high doses of antacid. Administration of CYTOTEC with a high fat content meal did not alter the extent of misoprostol absorption but did reduce the rate of absorption resulting in lower Cmax and higher tmax 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, attributed to the reduced clearance probably due partly to decreased volume of distribution and a slight prolongation of elimination $t_{1/2}$ of this

metabolite in the elderly. However, there were no significant differences in safety or ulcer healing efficacy in elderly patients (over 64 years) compared with younger patients.

5.3 Preclinical safety data

Genotoxicity and Carcinogenicity

There was no evidence of an effect of CYTOTEC on tumour occurrence or incidence in rats receiving daily doses up to 150 times (2400 micrograms/kg) the human dose for 24 months. Similarly, there was no effect of CYTOTEC on tumour occurrence or incidence in mice receiving daily doses up to 1000 times (16,000 micrograms/kg) the human dose for 21 months.

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

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

Hypromellose
Microcrystalline cellulose
Sodium starch glycollate
Hydrogenated castor oil

6.2 Incompatibilities

No data available.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Blister packs - Store at or below 25 °C. Protect from moisture.

Bottles – Store at or below 30 °C. Protect from moisture.

6.5 Nature and contents of container

CYTOTEC 200 mcg - Cold formed blister packs containing 10 or 120 tablets.

CYTOTEC 200 mcg - Bottles containing 12 or 120 tablets.

Not all presentations are marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

25 September 1986

10. DATE OF REVISION OF THE TEXT

29 May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance