AUSTRALIAN PRODUCT INFORMATION – CYTOTEC® (MISOPROSTOL)

1. NAME OF THE MEDICINE

Misoprostol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CYTOTEC tablets contain 200 micrograms of misoprostol

3. PHARMACEUTICAL FORM

Tablets 200 micrograms:

Scored, white, hexagonal tablets, debossed on one side with SEARLE/1461.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CYTOTEC is indicated in the treatment of acute duodenal and gastric ulcers.

CYTOTEC is indicated in the prevention of stress-induced upper gastrointestinal mucosal bleeding and lesions in post-surgical patients in intensive care units.

CYTOTEC is indicated for the prevention of gastric ulceration in patients in whom NSAID therapy is essential and who have been assessed at high risk of gastric ulceration, or the complications of gastric ulceration.

4.2 Dose and method of administration

Dosage

Treatment of Duodenal Ulcers:

800 micrograms per day in four divided doses with meals for four to eight weeks. The last dose should be taken at bedtime.

Treatment of Gastric Ulcers:

800 micrograms per day in four divided doses with meals for four to eight weeks. The last dose should be taken at bedtime.

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

200 micrograms every four hours for up to 14 days.

Prevention of NSAID-Induced Gastric Ulceration:

400 to 800 micrograms per day in divided doses with meals and at bedtime, taken simultaneously with the NSAID as appropriate. The NSAID should be taken according to the schedule prescribed by the physician. Cytotec may be administered for the duration of NSAID therapy. There are no data beyond 12 months to support the long-term efficacy for misoprostol for this indication.

Concomitant aluminium-containing antacids may be given as needed for relief of pain.

Dosage adjustment

Elderly

No dosage adjustment is recommended in older patients.

Use in Renal Impairment

Dosage may need to be reduced in patients with renal failure.

4.3 Contraindications

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

CYTOTEC is contraindicated in pregnancy, or in patients in whom pregnancy has not been excluded (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy and Section 4.8 Adverse effects (undesirable effects) - Post-marketing experience).

4.4 Special warnings and precautions for use

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.

Nosocomial Pulmonary Infections

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.

Use in renal impairment

Dosage may need to be reduced in patients with renal failure.

Use in the elderly

There were no significant differences in the safety profile of CYTOTEC in approximately 500 ulcer healing patients who were 65 years of age or older compared with younger patients.

Paediatric use

Safety and effectiveness in patients below the age of 18 have not been established.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

The serum protein binding of misoprostol acid was not affected by: indomethacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, paracetamol, ibuprofen, chlorpropamide, and hydrochlorothiazide.

With salicylic acid (300 micrograms/mL) the protein binding of misoprostol was lowered from 84% to 52% which is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short.

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 drugs normally metabolised by this system. No drug interactions have been attributed to misoprostol in extensive clinical trials. As such, other drugs would be unlikely to interfere with misoprostol's metabolism in either normal or hepatically impaired patients. There are no data on clinical safety beyond 12 months for the use of concurrent misoprostol and NSAIDs.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category X

Misoprostol is contraindicated in women who are pregnant because it induces uterine contractions and is associated with abortion, premature birth, and foetal death (see Section 4.3 Contraindications and Section 4.8 Adverse effects (undesirable effects) - Post-marketing

experience). 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. Women should be advised not to become pregnant while taking misoprostol. If a woman becomes pregnant while taking misoprostol, use of the product should be discontinued.

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 receiving CYTOTEC.

Use in 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.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

In clinical trials, the most frequent adverse events were diarrhoea, abdominal pain, and loose stools. These events occurred in approximately one-tenth of patients receiving CYTOTEC 800 micrograms daily in two or four divided doses. The events were usually transient and mild to moderate in severity. Diarrhoea, when it occurred, usually developed early in the course of treatment, was dose-related, self-limiting and required discontinuation of CYTOTEC in less than 2% of the patients, though it has occasionally been reported to lead to severe dehydration. The incidence of diarrhoea can be minimised by administering CYTOTEC immediately after meals and at bedtime, and by avoiding the use of magnesium-containing antacids. Dose adjustment may also be helpful. Abdominal pain has been associated with CYTOTEC therapy, and in controlled trials with concomitant NSAIDs the incidence was not significantly different from placebo.

Women who received CYTOTEC during clinical trials reported the following gynaecological disorders: uterine cramping, menorrhagia, menstrual disorder, spotting, dysmenorrhoea, intermenstrual bleeding, and vaginal haemorrhage (including postmenopausal bleeding). The incidence of each of these adverse reactions in women was <1%.

In clinical trials, the following adverse reactions were reported by more than 1% but less than 3% of the subjects receiving CYTOTEC and may be causally related to the drug: nausea, headache, flatulence, dyspepsia, vomiting, constipation and dizziness.

Elderly:

There were no significant differences in the safety profile of CYTOTEC in approximately 500 ulcer healing patients who were 65 years of age or older compared with younger patients.

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 foetal death have been reported when misoprostol was administered in pregnant women. CYTOTEC is contraindicated in pregnancy, or in patients in whom pregnancy has not been excluded (see Section 4.3 Contraindications and Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy).

Reproductive system and breast disorders: uterine haemorrhage.

Congenital, familial and genetic disorders: birth defects.

General disorders and administration site conditions: chills and pyrexia.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

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 foetal death.

The toxic dose of CYTOTEC 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.

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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia)..

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Acid Secretion

In the dosage range of 50 micrograms to 200 micrograms CYTOTEC inhibits gastric acid secretion in the basal state, as well as that stimulated by histamine, food and coffee. Additionally, CYTOTEC reduces nocturnal gastric acid secretion. The duration of inhibition of secretion is 3 to 6 hours.

In vitro studies indicate that the mechanism of gastric acid inhibition is mediated by a direct action on the parietal cells rather than by indirect mechanisms. 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. There was little or no effect on meal stimulated serum gastrin levels in animal studies. In human subjects, the rise in serum gastrin levels after a standard meal was sustained, probably as a consequence of reduced acid secretion.

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. At 25 micrograms and 50 micrograms, doses that exert little antisecretory effects, CYTOTEC showed mucosal cytoprotection in human subjects by reducing aspirin-induced gastric bleeding and by decreasing faecal blood loss when given concomitantly with aspirin.

In healthy subjects, pretreatment with the therapeutic dose of 200 micrograms CYTOTEC provided highly significant protection of the gastric mucosa against damage induced by a single dose of 1300 mg of aspirin. The same dose protected both gastric and duodenal mucosa against lesions induced by the non-steroidal anti-inflammatory agent, tolmetin (not marketed in Australia). In an ethanol-induced gastritis model in healthy subjects, CYTOTEC 200 micrograms provided significantly better protection than the antisecretory dose of 300 mg cimetidine, or a placebo.

While the mechanism of mucosal cytoprotection is not fully defined, CYTOTEC stimulated normal physiologic 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 micrograms increases human mucosal blood volume by more than 15% over baseline. In rats, mucosal blood flow is sustained, whereas, in dogs, it is increased.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

CYTOTEC is rapidly absorbed following oral administration, with peak plasma levels of the active metabolite (misoprostol acid) occurring in about 30 minutes, as measured either by radioactive or cold (Radioimmunoassay) methods. Misoprostol acid undergoes further metabolism by fatty acid oxidizing systems (beta and omega oxidation) which are present in numerous tissues in the body. The plasma elimination half-life of misoprostol acid is 20 - 40 minutes. The plasma elimination half-life of additional misoprostol metabolites is 1.5 hours.

Seventy-three percent of the radioactivity of an oral dose of radiolabelled misoprostol is excreted in the urine, 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, was in the range of 80 - 90% and was concentration-independent in the therapeutic range. There was no accumulation of misoprostol in red blood cells.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose

hypromellose

sodium starch glycollate

hydrogenated castor oil

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25° C and protect from moisture.

6.5 Nature and contents of container

The following presentations are registered: cold formed blister packs of 20 and 120* tablets and bottles of 12, 28, 60 and 120 tablets.

* Currently marketed pack size.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

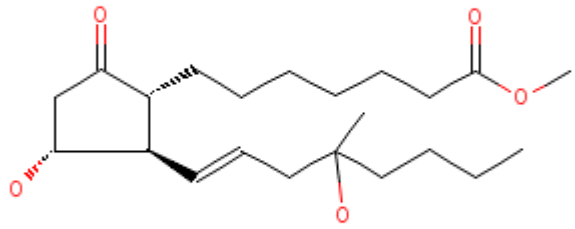
6.7 Physicochemical properties

Misoprostol is a water soluble, viscous liquid.

Misoprostol is a synthetic prostaglandin E_1 analogue. Misoprostol has a molecular formula of $C_{22}H_{38}O_5$ and a molecular weight of 382.5.

Chemical structure

The molecular structure of misoprostol is:



CAS number

59122-46-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription only medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229

www.pfizer.com.au

9. DATE OF FIRST APPROVAL

7 July 1993

10. DATE OF REVISION

25 November 2019

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
All	All sections reformatted in line with the new form.
3; 4; 5; & 6	Editorial
6.4	Storage conditions added
7	Medicine schedule added
8	Sponsor details updated