

CYTOTEC

Misoprostol 200 microgram tablet

PRESENTATION

Tablet uncoated scored, flat, white, hexagonal, with dimensions 0.830 cm x 0.919cm, debossed on one side with SEARLE 1461, each containing misoprostol 200 micrograms.

USES

Actions

CYTOTEC is a synthetic prostaglandin E₁ 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 **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS - Pregnancy and Lactation**).

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.

Pharmacokinetics

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 C_{max} and higher t_{max} 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.

Indications

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

CYTOTEC is indicated for the treatment of duodenal and gastric ulcers. 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.

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

DOSAGE AND ADMINISTRATION

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.

Elderly

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

Paediatric

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

CONTRAINDICATIONS

Misoprostol is contraindicated in women who are pregnant, or in patients in whom pregnancy has not been excluded (see **WARNINGS AND PRECAUTIONS – Pregnancy and Lactation** and **ADVERSE EFFECTS – Postmarketing surveillance**).

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

WARNINGS AND PRECAUTIONS

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.

Pregnancy and Lactation

Use in 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. 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 **CONTRAINDICATIONS** and **ADVERSE EFFECTS - Postmarketing Surveillance**).

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

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. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility, Teratology

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.

CYTOTEC is not foetotoxic 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 1000mcg/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/foetal loss was observed in rats given 10,000mcg/kg.

ADVERSE 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.

Postmarketing Surveillance

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 or in patients in whom pregnancy has not been excluded (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS - Pregnancy and Lactation**).

Reproductive system and breast disorders: uterine haemorrhage.

Congenital, familial and genetic disorders: birth defects.

General disorders and administration site conditions: chills and pyrexia.

INTERACTIONS

In clinical trials there was no evidence of interaction between CYTOTEC and cardiac, gastrointestinal, pulmonary, or CNS medicines (see also Pharmacokinetics). 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 of rheumatoid arthritis and osteoarthritis.

OVERDOSAGE

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 foetal 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.

Contact the Poisons Information Centre for advice on the management of an overdose.

PHARMACEUTICAL PRECAUTIONS

Store below 25° C. Protect from moisture.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

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

FURTHER INFORMATION

Excipients: hypromellose, microcrystalline cellulose, sodium starch glycollate, hydrogenated castor oil.

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

The chemical name is (+) methyl 11 α ,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate. The chemical formula of misoprostol is C₂₂H₃₈O₅ and the molecular weight is 382.5.

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

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