PRODUCT MONOGRAPH

MISOPROSTOL

Misoprostol Tablets

100 mcg and 200 mcg

Mucosal Protective Agent

AA PHARMA INC.
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Control #: 138783

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THERAPEUTIC CLASSIFICATION

Mucosal Protective Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Misoprostol is a synthetic analogue of prostaglandin E_1. In animals and man, orally administered misoprostol has both gastric antisecretory and mucosal protective effects. Its antisecretory activity is mediated by misoprostol acid binding to specific prostaglandin receptors on gastric parietal cells. The mechanism of the gastrointestinal mucosal protective effect of misoprostol is not as well understood, but is thought to involve the replacement of prostaglandins following their depletion or inhibition of production, the increasing of mucus production, the increasing of bicarbonate secretion in the duodenum, increased mucosal blood flow, decreased vascular permeability, increased cellular proliferation and migration, and the restoration of the gastric potential difference. Studies conducted in animals and clinical trials in humans have demonstrated that misoprostol can protect the gastric mucosa against various irritants such as alcohol, acetylsalicylic acid, naproxen, tolmetin and sodium taurocholate.

Misoprostol is a prodrug for the active de-esterified misoprostol acid. Conversion to misoprostol acid occurs rapidly in the stomach. The misoprostol acid then binds locally to receptors (e.g. on the parietal cells), undergoes additional hydrolysis, is taken up and metabolized by cells lining the stomach or in the liver, or is passed on to the small intestine along with stomach contents.

In a recent cross-over study (1995), a single 200 mcg oral dose of misoprostol administered to sixteen fasting, healthy male subjects produced mean C_{max}, AUC (0-24), T_{max} and elimination half-life of misoprostol acid of: 206.5 pg/mL, 141.8 pg.hr/mL, 0.42 hours, and 0.48 hours respectively. The values of these pharmacokinetic parameters differ from those which were obtained from a pilot study conducted in 1984 (as previously reported). For details, see information presented in the section ñCLINICAL PHARMACOLOGY: Pharmacokineticsò. Despite the low systemic bioavailability of misoprostol (~7%), misoprostol acid is very potent and even these sub-nanomolar systemic concentrations may elicit prostaglandin-like effects in other tissues. These effects have been associated with diarrhea uterine contractions and menstrual irregularities.

Misoprostol has both local and systemic activity. Although misoprostol systemic $t_{1/2}$ is very short with plasma levels not typically detectable beyond 2 hours, the duration of its activities, e.g. antisecretory properties, in the gastric tissues are greater than 3 but less than 6 hours. (See CLINICAL PHARMACOLOGY.)

Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $t_{1/2}$, C_{max}, and AUC compared to normals, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of misoprostol was measured and compared following oral administration of 400 mcg (two MISOPROSTOL 200 mcg tablets or two Cytotec 200 mcg tablets). The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Misoprostol (Dose: 400 mcg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%) MISOPROSTOL	Cytotec®	Ratio of Geometric Means (%)**
AUC_T (pgXhr/mL)	561 585 (33)	588 615 (31)	95.4
AUC_I (pgXhr/mL)	588 610 (31)	614 638 (29)	95.8
C_{max} (pg/mL)	242 267 (48)	251 273 (47)	95.2
T_{max} (hr)*	0.97 (120)	0.66 (72)	--
$t_{1/2}$ (hr)*	0.88 (49)	0.77 (51)	--

* Arithmetic means (CV%).
** Based on the least squares estimate.
Cytotec® (Searle Canada) was purchased at a Canadian retail pharmacy.

INDICATIONS AND CLINICAL USE

MISOPROSTOL (misoprostol) is indicated for the treatment and prevention of NSAID-induced gastroduodenal ulcers. MISOPROSTOL is also indicated for the treatment of duodenal ulcers caused by Peptic Ulcer Disease (PUD).

Patients at high risk of developing NSAID-induced complications and who may require protection include:

- Patients with a previous history of ulcer disease or a significant gastrointestinal event.
- Patients over 60 years of age.
- Patient judged to be at risk because of general poor health, severe concomitant medical disease, or patients who are poor surgical risks.
- Patients disabled by joint symptoms (e.g. HAQ Disability Index Score > 1.5) or those with severe systemic manifestations of arthritis.
- Patients taking other drugs known to damage or exacerbate damage to the gastrointestinal tract such as corticosteroids or anticoagulants.
- Patients taking a high dosage or multiple NSAIDs, including those available Over-The-Counter.

The risk of NSAID-induced complications may be highest in the first three months of NSAID therapy.

CONTRAINDICATIONS

Known sensitivity to prostaglandins, prostaglandin analogues, or excipients.

MISOPROSTOL (misoprostol), or misoprostol in any form, should not be used in pregnant women because it induces uterine contractions and therefore has abortifacient potential. Anecdotal reports, primarily from Brazil, of congenital anomalies and reports of fetal death

subsequent to misuse of misoprostol as an abortifacient have been received. Uterine perforation has been reported with misuse of misoprostol for cervical ripening or labor induction.

Women of childbearing potential should not be started on MISOPROSTOL until pregnancy is excluded, and should be fully counseled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, use of the product should be discontinued.

WARNINGS

Women of childbearing potential should employ adequate contraception (i.e., oral contraceptives or intrauterine devices) while receiving MISOPROSTOL (misoprostol) (see CONTRAINDICATIONS).

Nursing Mothers: It is unlikely that misoprostol is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, MISOPROSTOL should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

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

PRECAUTIONS

Selection of Patients: Caution should be used when using symptomatology as the sole diagnosis and follow-up procedure, since misoprostol has not been shown to have an effect on gastrointestinal pain or discomfort.

When misoprostol is used for the treatment of ulcers, a positive diagnosis of duodenal ulcer or NSAID-induced gastroduodenal ulcer should be made. The general health of the patient should be considered. Misoprostol is rapidly metabolized by most body tissues to inactive metabolites. Nevertheless, caution should be exercised when patients have impairment of renal or hepatic function (see CLINICAL PHARMACOLOGY; Pharmacokinetics).

Diarrhea: Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as irritable bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if MISOPROSTOL (misoprostol) is prescribed.

Use in Elderly or Renally Impaired: Considerations for Dosage Adjustment: In subjects over 64 years of age or those who are renally impaired the pharmacokinetics may be affected, but not to a clinically significant degree (see DOSAGE and ADMINISTRATION). No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 mcg QID) is recommended.

Drug Interactions: No clinically significant drug interactions attributable to misoprostol have been observed to date. (See CLINICAL PHARMACOLOGY).

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

Salicylic acid (300 mcg/mL) lowered the protein binding of misoprostol from 84% to 52%; this is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination halfi life is very short.

In laboratory studies, misoprostol has shown 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 metabolized by this system.

Misoprostol does not interfere with the beneficial effects of NSAIDS on the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Magnesium containing antacids may increase the likelihood of diarrhea.

Some prostaglandins and prostaglandin analogues have the capacity to produce hypotension through peripheral vasodilation. MISOPROSTOL 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. Therefore, misoprostol tablets should be used in known epileptics only when their epilepsy is adequately controlled and then only when expected benefits outweigh potential risks.

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.

Keep MISOPROSTOL out of the reach of children.

ADVERSE REACTIONS

Gastrointestinal: In subjects and patients receiving at least one dose of misoprostol in clinical trials, the most frequent gastrointestinal adverse events were diarrhea (14.6%), abdominal pain (12.7%), nausea (7.3%), flatulence (6.8%), dyspepsia (6.3%), vomiting (2.3%) and constipation (1.7%). The events were usually transient and mild to moderate in severity.

Diarrhea and abdominal pain, when they occurred, usually developed early in the course of therapy, were self limiting and required discontinuation of misoprostol in less than 5% of the patients. Diarrhea is dose related. The incidence of diarrhea can be minimized by reducing the dose of misoprostol, by administering immediately after a meal or with food or milk, and by avoiding co-administration of misoprostol with magnesium-containing antacids.

Gynecological: Women who received misoprostol during clinical trials reported the following gynecological disorders: spotting, uterine cramps, menorrhagia, menstrual disorder, dysmenorrhea and vaginal hemorrhage (including postmenopausal bleeding). The incidence of each of these adverse events in women was <1%. The overall incidence of gynecological disorders was lower in women over 50 years of age.

Elderly: In clinical trials, 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.

Confusion has been reported in a small number of patients in post-marketing surveillance of misoprostol.

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving misoprostol: headache and dizziness. However, there were no clinically significant differences between the incidences of these events for misoprostol and placebo.

The profile for adverse reactions with Ó1% incidence was similar for short-term (four to twelve weeks duration) and long-term (up to one year) clinical trials. Therefore, misoprostol may be administered for up to one year without expecting an increase in adverse events. This includes no adverse or unusual change in the morphology of gastric mucosa, as determined by gastric biopsy.

Adverse reactions reported from post-marketing experience are consistent with those reported from clinical trials.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The toxic dose of misoprostol in human beings has not been determined. Cumulative total daily doses of 1,600 mcg have been tolerated with only symptoms of gastrointestinal discomfort being reported. In animals, the acute toxic effects are similar to those reported for other prostaglandins and prostaglandin analogues: relaxation of smooth muscle, respiratory difficulties, and depression of the central nervous system. Possible clinical signs that may indicate an overdose may include: sedation, tremor, fever, convulsions, dyspnea, abdominal pain and cramping, severe or profound diarrhea, palpitations, hypotension, or bradycardia. Treatment should be symptomatic and supportive.

It is not known if misoprostol acid is dialyzable. However, because misoprostol has a large volume of distribution and is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

DOSAGE AND ADMINISTRATION

MISOPROSTOL (misoprostol) should be taken with food or milk. To minimize the risk of diarrhea, magnesium-containing antacids should be avoided. Aluminum-based antacids may be used as needed for relief of heartburn/epigastric pain.

Treatment and Prevention of NSAID-Induced Gastroduodenal Ulcers: The recommended adult oral dose of MISOPROSTOL for the prevention and treatment of NSAID-induced gastroduodenal ulcer is 400 to 800 mcg a day in divided doses. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate, MISOPROSTOL and NSAIDs are to be taken simultaneously. MISOPROSTOL should be taken after a meal or with food or milk.

Treatment of Duodenal Ulcer: The recommended adult oral dose of MISOPROSTOL for duodenal ulcer is 800 mcg per day for 4 weeks in two or four equally divided doses (i.e., 200 mcg qid or 400 mcg bid). The last dose should be taken at bedtime with food. Treatment should be continued for a total of 4 weeks unless healing in less time had been documented by endoscopic examination. In the small number of patients who may not have fully healed after 4 weeks, therapy with MISOPROSTOL may be continued for a further 4 weeks.

Use in Elderly and Renally Impaired: Consideration for Dosage Adjustment: Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $t_{1/2}$, C_{max} and AUC compared to normals. There was no clear correlation between degree of impairment and AUC. In subjects over 64 years of age, the pharmacokinetics may be affected.

In both patient groups, the pharmacokinetic changes are not clinically significant. No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 mcg QID) is recommended.

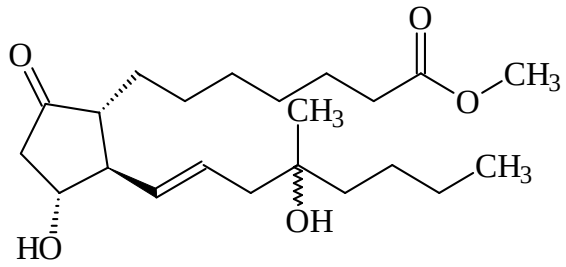
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Misoprostol

Chemical Name: (±) methyl (11α, 13E)-11, 16-dihydroxy-16-methyl-9-oxoprost-13-en-1ï oate

Structural Formula:



Molecular Formula: $C_{22}H_{38}O_5$

Molecular Weight: 382.5

Description: Misoprostol is a novel synthetic prostaglandin E_1 analogue. It is a light yellow, viscous liquid with a musty odour.

Composition

In addition to misoprostol, each tablet contains the non-medicinal ingredients microcrystalline cellulose, hydroxypropyl methylcellulose, croscarmellose sodium and magnesium stearate.

Stability and Storage Recommendations

Store between 15° and 30°C, protect from humidity. Keep container closed when not in use.

AVAILABILITY OF DOSAGE FORMS

100 mcg: Each round, white, flat-faced, beveled-edged tablet engraved ñMISOò over ñ100ò on one side contains 100 mcg misoprostol. Available in bottles of 100, 250 and 500.

200 mcg: Each hexagonal, white, flat-faced, beveled-edged tablet scored and engraved ñMISOò over ñ200ò on one side contains 200 mcg misoprostol. Available in bottles of 100 and 500.

INFORMATION FOR THE PATIENT

What is MISOPROSTOL?

MISOPROSTOL (also called misoprostol) is the only medicine approved in Canada for the treatment and primary prevention of gastroduodenal damage caused by arthritis medicines called NSAIDs. Gastroduodenal damage refers to damage in either the stomach or duodenum. Your duodenum is the small portion of the intestine that is immediately adjacent to the stomach.

What is a NSAID?

NSAID is an abbreviation for ñon-steroidal anti-inflammatory drugò ñNon-steroidalòmeans that this type of medicine does not contain steroids, such as cortisone or prednisone. ñAnti-inflammatoryòmeans that the medicine works by decreasing inflammation.

NSAID medicines are commonly prescribed to treat the pain and inflammation of arthritis and certain muscle conditions. While NSAIDs have many benefits, unfortunately they can cause stomach and gastrointestinal ulcers in some people. These ulcers often appear without any pain or warning symptoms.

Why Do NSAIDs Sometimes Cause Ulcers?

Your body contains a mucous layer on the inside of the stomach and intestine to protect it from stomach acids and digestive juices needed to digest food. The body produces natural substances called ñprostaglandinsòto keep this layer intact.

NSAIDs are believed to treat arthritis by lowering the amount of ñprostaglandinsò This has a good effect on the joints by helping to decrease the pain, redness and swelling of arthritis. Unfortunately, NSAIDs can also thin the protective mucous layer inside the stomach. The stomach can then become more prone to developing ulcers.

Who Is At Risk?

You may be at higher risk of developing a NSAID-ulcer if you must continue taking arthritis medicine and you:

- are older than 60 years of age
- have had stomach upset in the past while taking NSAID medicines
- have had a stomach ulcer(s)
- are taking high doses of NSAIDs or multiple dosages of NSAIDs including taking Over-The-Counter NSAIDs such as A.S.A. or ibuprofen
- are taking certain other medicines such as corticosteroids or anticoagulants that are known to either damage the stomach or worsen the outcome of a damaged stomach
- have other serious medical conditions or are in poor health
- are severely disabled by an arthritic condition.

In addition, you may be at greater risk in the first three months after starting your NSAID.

How Does MISOPROSTOL Work?

MISOPROSTOL is a manufactured prostaglandin similar to the prostaglandins found naturally in your body. MISOPROSTOL replaces the prostaglandins that your body is losing while you are taking the NSAID medicine. In doing this, MISOPROSTOL helps protect your stomach and duodenum.

MISOPROSTOL helps protect your stomach and duodenum from NSAID ulcers in two ways:

- It protects the mucous layer on the inside of your stomach.
- It decreases the amount of acid that may irritate the lining of your stomach and duodenum.

MISOPROSTOL makes it possible for you to continue taking the NSAID medicine for your arthritis by protecting your stomach and duodenum.

MISOPROSTOL is also used to help heal duodenal ulcer.

How Do You Take MISOPROSTOL?

DO Take each dose of MISOPROSTOL immediately after a meal or with food or milk. This will help prevent gastrointestinal disturbances (e.g. loose stools, diarrhea, and abdominal cramping) that may occur in the first few days of therapy.

DO Continue to take MISOPROSTOL if you develop these symptoms. Do not be alarmed. This is part of the effect of the medicine which your body is adjusting to. Keep taking MISOPROSTOL. These symptoms will usually disappear within a few days.

DO Call your doctor if these symptoms become bothersome or do not go away within one week.

DONõT Do not take antacids that contain magnesium while you are taking MISOPROSTOL. Ask your doctor or pharmacist for help in selecting a suitable antacid.

DONõT Do not share MISOPROSTOL with anyone.

DO Keep MISOPROSTOL and all other medicines out of the reach of children.

DONõT Do not take MISOPROSTOL if you are allergic to prostaglandins.

Special Note for Women of Childbearing Age

MISOPROSTOL may cause a miscarriage or may otherwise harm the unborn developing baby. Therefore, if you are pregnant, you must not take this drug.

Miscarriages caused by MISOPROSTOL are likely to be incomplete. An incomplete miscarriage may result in very serious medical complications, resulting in hospitalization, surgery and possible infertility.

If you think your are pregnant, you must not take MISOPROSTOL. You should avoid becoming pregnant while you are taking MISOPROSTOL. This means using an effective form of birth control. Stop taking MISOPROSTOL, and contact your doctor immediately if you do become pregnant during MISOPROSTOL therapy.

You should not take MISOPROSTOL if you are nursing because the potential excretion of misoprostol acid could cause diarrhea in nursing infants.

Adult Dosage

For treatment and prevention of non-steroidal anti-inflammatory drug induced gastroduodenal ulcer: 400 to 800 mcg per day in divided doses. Treatment of duodenal ulcer: 800 mcg daily in two or four equally divided doses. Take after food. Not recommended for patients under 18 years of age.

Storage

Store between 15° and 30°C, protect from humidity. Keep container closed when not in use.

PRECLINICAL PHARMACOLOGY

Misoprostol is rapidly de-esterified to the free acid following ingestion. The free acid interacts with gastrointestinal prostaglandin receptors, is absorbed, or is metabolized by gastrointestinal cells, the liver and other tissues. In all species examined, misoprostol acid was metabolized to inactive metabolites by beta oxidation of the alpha chain, omega oxidation of the beta chain, and to F prostaglandin analogs. The majority of these metabolites was excreted in the urine (30-63%) rather than in the feces (21-48%). The dog appears most similar to man with respect to the amount of radiolabel excreted in urine (58.4%) and the urinary to fecal excretion ratio (2.8). No misoprostol acid has been detected in the urine of humans, although 1-4% of the dose has been recovered in the urine of dogs and rats.

Misoprostol did not alter liver microsomal cytochrome P-450 concentrations or mixed function oxidase activities measured *in vitro*. The enzyme systems which metabolize the free acid of misoprostol are primarily those that metabolize fatty acids (e.g., beta oxidation) rather than the mixed function oxidases which metabolize most drugs.

Misoprostol reacts rapidly with the gastric mucosa; histologically detectable changes consistent with cytoprotective activity are detectable within 5 minutes, even with low (10 ng/mL) concentrations of misoprostol applied to dog gastric mucosa. The magnitude of the effects is dose dependent. The protective effect on the gastric mucosal barrier in dogs lasts beyond the presence of detectable misoprostol serum concentrations. Studies in the rat using pyloric ligation and in the dog using a variety of secretagogues (e.g., histamine, pentagastrin and food) show the

ability of misoprostol to reduce gastric acid secretion by reduction of hydrogen ion concentration. Volume of gastric secretion was also reduced in the dog. The use of an innervated gastric pouch dog model (Pavlov), in addition to a denervated model (Heidenhain) for the food stimulation studies, showed that intact nervous system reflexes are not required for activity.

Misoprostol promotes mucus production and secretion, and cellular swelling at concentrations substantially below those needed for antisecretory activity. These changes are not accompanied by vascular constriction, but display evidence of misoprostol-induced vasodilation. A direct local action on the parietal cells is also supported by the lower dose required to block gastric acid secretion when misoprostol is put directly into the pouch, as opposed to the dose required when the misoprostol must reach the pouch via the systemic circulation. Application of misoprostol to isolated canine parietal cells *in vitro* blocked acid secretion induced by histamine, but not that induced by dibutyryl cAMP. The antisecretory action of misoprostol can be produced by misoprostol acid in the stomach, and appears to be exerted between the histamine receptor activation and the formation of cAMP. Misoprostol does not lower serum gastrin levels indicating that its antisecretory effects are not mediated by this mechanism.

Local vasodilation is consistent with the observation that misoprostol does not decrease, but rather may increase gastric mucosal blood flow.

Misoprostol prevented gastric ulcers or lesions induced in various species by a variety of chemical insults (indomethacin, pentagastrin, histamine, ethanol and taurocholate) or procedures (ligation and forced exertion stress). Results from concentration response studies and from various insult models indicate that the mucosal protective activity and the antisecretory activities of misoprostol acid, like other prostaglandins, are separate, but perhaps complimentary. The

mucosal protective activity of misoprostol was effective at doses less than 10% of the gastric antisecretory dose in both acid dependent and acid independent ulcer models.

The potential of misoprostol to cause diarrhea, an expected side effect of E-type prostaglandins, is separate from its cytoprotective and antisecretory activities, and dependent on the release characteristics of the formulation. The intragastric diarrheogenic dose (366-1305 mcg/kg) of misoprostol in the rat is 10 to 30 times the antiulcer dose (10-30 mcg/kg).

CLINICAL PHARMACOLOGY

Antisecretory Activity

Effect on Acid Secretion: When compared to placebo in healthy subjects, misoprostol 200 mcg inhibited basal acid secretion by 100%, decreased nocturnal acid secretion by 50% during hours 2 and 3 post-dose ($p<0.05$), reduced total acid output during the first 30 minutes of histamine stimulation ($p < 0.05$) and reduced total meal-stimulated acid output over a 3-hour test period ($p<0.05$). In healthy human subjects misoprostol inhibits acid secretion stimulated by pentagastrin, tetragastrin, betazole and coffee. Although misoprostol systemic $t_{1/2}$ is very short with plasma levels not typically detectable beyond 2 hours, the duration of its activities, e.g. antisecretory properties, in the gastric tissues are greater than 3 but less than 6 hours.

Effect on Pepsin Secretion: A moderate decrease (30-80%) in pepsin concentration was seen under basal conditions, but not during histamine stimulation.

Effect on Serum Gastrin and Volume of Gastric Fluid: Misoprostol had no significant effect on fasting levels or post-prandial increases of serum gastrin, or on the volume of gastric fluid. Misoprostol decreases pepsin output, gastric acid output and gastric fluid volume under basal conditions, and under some stimulated conditions.

Mucosal Protective Activity

In 12 healthy subjects, 50 mcg of misoprostol significantly reduced gastric bleeding, previously induced by ingestion of high doses of ASA (975 mg qid). Misoprostol 25 mcg administered concomitantly with high doses of ASA (650 mg qid) to 32 healthy subjects significantly reduced gastric blood loss.

A further doubleï blind randomized study using an ASA-model was conducted in 60 normal volunteers. Each subject received either misoprostol 200 mcg qid or placebo for five doses.

Thirty minutes after the last dose, subjects ingested four ASA tablets (1296 mg), and two hours later endoscopy was performed. Twenty of the thirty misoprostol treated subjects were protected against gastric injury (as determined by endoscopic scores) as compared with one of 30 subjects who received placebo ($p<0.001$).

A study using a different non-steroidal anti-inflammatory drug, tolmetin, was then conducted. Sixty healthy subjects received tolmetin (2,000 mg/day) and either misoprostol (200 mcg) or placebo in four divided doses for six and a quarter days. Two hours after the last dose, an endoscopic examination was performed. In the placebo group, 7 of 29 subjects (24%) were considered treatment successes (10 or fewer hemorrhages or erosions). In the misoprostol group, 27 of 30 (90%) were treatment successes ($p<0.005$). Misoprostol was also significantly more effective ($p= 0.02$) than placebo in protecting the duodenal mucosa against tolmetin damage (93.3% vs. 70.0%).

In an ethanol-induced gastritis model in 45 healthy subjects, a single daily dose of misoprostol 200 mcg prevented gastric mucosal injury, as determined by an endoscopic score, when compared with placebo ($p=0.0001$) and 300 mg cimetidine ($p=0.0002$). This mucosal protective

activity is additional to the inhibition of gastric acid secretion. The mucosal protective activity is also significantly greater than that seen with a fully antisecretory dose of cimetidine.

The effects of misoprostol on gastric acid and mucus secretion were compared to those of placebo in eight healthy volunteers. Mucus secretion increased by 37%, 82%, ($p<0.05$), and 95% ($p<0.01$) during the basal period following administration of misoprostol 200, 400 and 800 mcg, respectively. Misoprostol at 200, 400 and 800 mcg doses increased mucus secretion during the period of maximal acid inhibition (1 to 30 minutes after pentagastrin administration) by 27%, 31% and 38% ($p<0.05$), respectively.

A study was conducted in five healthy male volunteers to determine the effect of misoprostol on human duodenal mucosal bicarbonate secretion. Graded doses of misoprostol from 50 to 400 mcg stimulated proximal and distal duodenal bicarbonate secretion approximately 3 and 7 fold, respectively. At each dose, bicarbonate secretion was significantly greater in the proximal versus the distal duodenum.

Pharmacokinetics

Misoprostol is rapidly de-esterified to the biologically active misoprostol acid after ingestion. No intact misoprostol is detected in the plasma, or recovered in the urine of humans. Tablet dissolution is rapid. Early accessibility of the misoprostol to gastric tissues is thought to be critical to maximal cytoprotective effect. Misoprostol acid undergoes further metabolism by beta oxidation of the alpha chain, omega oxidation of the beta chain, and conversion to F prostaglandin analogs. This metabolism to inactive forms can take place in numerous tissues, including gastrointestinal tissues and liver.

In a recent single dose cross-over study in 16 male volunteers (1995) to assess the absolute bioavailability of misoprostol, 20 mcg of misoprostol administered as a 0.33 hour infusion produced a mean AUC of 186.5 pg.hr/mL, while 200 mcg administered orally produced a mean AUC of 141.8 pg.hr/mL. The mean peak concentration for the IV infusion was 470.5 pg/mL and occurred at 0.33 hours (the end of the infusion), while the mean peak concentration after the oral dose was 206.5 pg/mL and occurred at 0.42 hours. The terminal half-lives were 0.43 and 0.48 hours. These pharmacokinetic parameters are summarized in Table 1. The data suggest that the volume of distribution of misoprostol acid is approximately 40 liters in humans.

Table 1: Misoprostol Acid Pharmacokinetic Parameters

	Misoprostol (I.V.)	Misoprostol (oral)
AUC (mean) (pg.hr/mL)	186.5	141.8
C_{max} (mean) (pg/mL)	470.5	206.5
T_{max} (mean) (hr)	0.34	0.42
$T_{1/2}$ (mean) (hr)	0.43	0.48

In an early pilot study (1984), 200 mcg of oral misoprostol were administered to 6 male volunteers to learn whether misoprostol acid concentrations would even be detectable in human plasma following a standard oral dose using the available assay technology. The observed concentrations were low by detectable providing a mean C_{max} of 309 pg/mL, a mean AUC of 355 pg hr/mL, a mean $T_{1/2}$ of 0.33 hours and a mean T_{max} at 0.5 hr.

In another pilot study (1984), a single dose of 200 mcg of tritiated-misoprostol in solution was administered to six healthy male subjects. The major portion (64% to 73%) of the orally administered radioactive dose was excreted in the urine within the first 24 hours, with 56% being excreted in the first 8 hours. An additional 15% was excreted in the feces in 24 hours. The

results indicate that a large portion of the administered radioactivity was absorbed. None of the parent misoprostol, however, can be detected in the plasma following oral dosing, and only about 7% of the dose appears in the systemic circulation as the misoprostol acid. These observations are consistent with the rapid de-esterification of the parent drug in the gastric fluid, and subsequent metabolism of the misoprostol acid by pathways normally associated with prostaglandin and fatty acid metabolism in a variety of tissues in the body. The low systemic bioavailability of misoprostol acid does not impact efficacy since the desired cytoprotective activity occurs in the gastrointestinal tract, and does not require misoprostol absorption into the circulation.

The serum protein binding of misoprostol acid was not extensive (less than 90%) and was concentration independent in the therapeutic range. There was no accumulation of misoprostol in the red blood cells. The serum protein binding of misoprostol acid was unaffected by the drugs listed in Table 2.

Table 2: Drugs Not Affecting The Serum Protein Binding of Misoprostol

Indomethacin	Propranolol
Ranitidine	Triamterene
Digoxin	Cimetidine
Phenylbutazone	Acetaminophen
Warfarin	Ibuprofen
Diazepam	Chlorpropamide
Methyldopa	Hydrochlorothiazide

With salicylic acid (300 mcg/mL) the protein binding 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.

Laboratory studies have demonstrated that misoprostol does not inhibit or induce the following drug metabolizing enzyme systems:

- Cytochrome P450
- Aminopyrine Demethylase
- Hexobarbital Hydroxylase
- p-Nitroanisole 0-Demethylase

It is therefore unlikely that the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolized by these systems would be altered in clinical situations. In clinical studies conducted to date involving almost 6,000 patients, no drug interactions attributable to misoprostol have been observed.

Uterotropic Effect

Natural and synthetic prostaglandins have known effects on the pregnant human uterus. Two studies were conducted to evaluate this effect. The study populations included pregnant females who had previously elected to terminate pregnancy during the first trimester. Two doses of misoprostol (400 mcg) were administered four to five hours apart.

In one study, misoprostol caused an increase in the frequency and intensity of uterine contractions and frequency of uterine bleeding (misoprostol 1/4, placebo 0/4). In the second study, misoprostol administration was associated with a higher incidence of uterine bleeding [placebo: 2/55 (4%) and misoprostol: 25/56 (45%)] and expulsion of the uterine contents

[placebo: 0/55 (0%) and misoprostol 6/56 (11%)]. Misoprostol can produce uterotropic activity whether administered orally or intra-vaginally.

Immunologic Effect

Immunologic competence is not modified by recommended doses of misoprostol.

TOXICOLOGY

Acute Toxicity

Single dose studies in rodents indicate a safety margin of at least a thousand fold between doses lethal to animals and the human therapeutic dose. LD_{50} values (mg/kg) in male and female animals were as follows:

Oral	-	rats:	81-100
		mice:	27-138
Intraperitoneal	-	rats:	40-62
		mice:	70-160

No deaths occurred in dogs at oral dosages up to 10 mg/kg in an escalating dose study. In rodents, most deaths occurred within 24 hours and most surviving animals appeared normal within three to four days after dosing.

There were no marked sex-related differences in LD_{50} values or in the occurrence of clinical signs in any species by any route. The most prominent clinical signs in rodents were reduced motor activity and diarrhea. Common clinical signs in the dog were emesis, tremors, mydriasis and diarrhea.

Drug related hypertrophy of mucus cells and deepening of gastric pits were found in dogs by microscopic examination.

Acute oral toxicity studies in male mice at a single dosage of 5,000 mcg/kg were conducted with misoprostol degradation products (SC-29636, SC-32759, and SC-33188). There were no deaths or other clinical observations associated with these compounds in the acute studies.

Chronic Toxicity

Studies in Dogs: Two, 5, 13 and 52 week toxicity studies were conducted in beagle dogs at daily oral dosages ranging from 30 to 1,000 mcg/kg/day. The 13 and 52 week studies included a drug free recovery period.

The most prominent clinical signs were emesis, diarrhea, soft and/or mucoid stools and increased rectal temperatures. The mucoid stools may be due to hyperplasia of mucin producing cells of the stomach. The clinical observations were generally dose-related in incidence and severity and either decreased or were absent at the end of the reversal periods. The pyrogenic and diarrheogenic activity observed are characteristic of some prostaglandins. There were no drug related findings in the ophthalmic and electrocardiographic tests.

Deaths occurred at dosages as low as 300 mcg/kg. Of the two animals that died at this dosage, one probably died of asphyxiation following aspiration of vomitus and the other was killed in extremis during the first week of the study because it had stopped eating.

An apparent increase in estrus activity seen in the thirteen week study was not confirmed in the one year study. The age of the animals in the thirteen week study coincided with the time of first

estrus which is known to occur in a highly variable manner. The gross and microscopic pathology findings in the ovaries and uterus were normal changes accompanying estrus.

Clinical laboratory changes, with the exception of a slight increase in chloride concentrations, were incidental and/or within normal physiological variation. In the fifty-two week study, mean chloride concentrations were increased approximately 2, 4 and 5% at 30, 100 and 300 mcg/kg dosages, respectively. These increases were statistically significant only in female animals. There were no abnormal clinical laboratory findings at the end of the reversal periods.

Radiographic examination of long bones was performed after 10 months in the 52 week toxicity study. No significant differences were noted between misoprostol treated and control animals. At the end of the dosing, gross examination of the skeleton was done, along with a microscopic examination of the femur, tibia, and humerus. There was no evidence of hyperostosis.

Reversible gastric mucosal epithelia hyperplasia accompanied, in some cases, by excessive mucus was a consistent gross and microscopic change in the dog studies. The hyperplasia, present at all dosages in the 52 week study, was reflected in increased stomach weights and stomach to body weight ratios. Other changes in organ weights and/or ratios were not meaningful. In the 52 week study, there was no ultrastructural difference between gastric surface mucus cells of control animals and animals given misoprostol 300 mcg/kg/day.

After a four week recovery period in the 13 week study, a slight villous epithelial hyperplasia remained in the 480 mcg/kg group. After a three month recovery period in the 52 week study, there were no gross changes in the stomach and only one 300 mcg/kg group male dog had hyperplasia of the pyloric epithelium.

Studies In Rats: Two, 4, 5, 13 and 52 week toxicity studies were done in rats at daily oral dosages up to 9,000 mcg/kg.

The most prominent clinical signs were diarrhea, salivation, vaginal dilation and discharge, decreased body weight gain (mainly males) and increased food consumption. The diarrhea and vaginal dilation are ascribable to the known effect of some prostaglandins on smooth muscle. There were no treatment related ophthalmic changes. In the 52 week study, there were no abnormal clinical signs at 160 mcg/kg and all signs at the higher doses were absent at the end of a 13 week reversal period.

The deaths that occurred in the various studies were not considered drugï related.

Clinical laboratory changes included decreases in serum total protein and increases in serum iron. Other changes were either incidental and/or within normal physiological variation. In the 52 week study, serum total protein decreased approximately 7-11% at 9,000 mcg/kg. This decrease may be due to poor absorption of protein constituents resulting from diarrhea. Serum iron was significantly increased at 9,000 mcg/kg in one 5 week study and in the 52 week study, and at 1,600 and 8,000 mcg/kg in the other 5 week study. This change was accompanied by a decrease in unsaturated iron binding capacity and an increase in the iron saturation index. In the 52 week study there were no meaningful clinical laboratory changes at 1,200 mcg/kg and the changes observed at 9,000 were absent at the end of the reversal period.

Hyperkeratosis of the aglandular part of the stomach and mucosal epithelial hyperplasia of the glandular part were the prominent gross and microscopic changes at all dosages in the 52 week study. In addition, hyperplasia of the superficial epithelial cells of the colon was also observed in

a few animals at 9,000 mcg/kg. These microscopic changes were absent at the end of the reversal period.

The morphologic changes in the stomach were reflected in increased stomach weights and stomach to body weight ratios in the 52 week study.

Electron microscopy of the stomach mucosa of some control and 9,000 mcg/kg animals from the 52 week study showed the aglandular part of the stomach of treated animals had increased numbers of loose keratin layers (hyperkeratosis) on the mucosal surface but the mucosal cells and keratin had normal structure. The glandular mucosa (corpus and antrum) of the 9,000 mcg/kg rats had increased depth of gastric pits. Slight differences were noted in the quantity and characteristics of mucus granules in some mucus secreting cells of these areas. There were no differences in other cell types. Additional changes in organ weights and/or organ to body weight ratios, which were not accompanied by any abnormal microscopic findings, occurred mainly at 9,000 mcg/kg and were absent after the reversal period. There was no evidence of hyperostosis in any of the treatment groups.

Reproduction Studies

Fertility (Segment I) and perinatal/postnatal (Segment III) studies in rats and teratology (Segment II) studies in rats and rabbits were performed. In general, there were drug-related clinical signs of salivation, soft feces, lethargy, and unkempt appearance at the higher doses of misoprostol. At a dosage of 100 mcg/kg, no drug-related clinical signs occurred.

Although no drugï related deaths occurred, toxicity was observed at 1,600 mcg/kg and above in rats and 300 mcg/kg and above in rabbits as evidenced by the adverse effect on body weights of male or female animals given misoprostol.

In two rat fertility studies, the number of implantations was decreased at 1,600 mcg/kg and above. An increased number of resorptions occurred at 1,000 and 10,000 mcg/kg in one study but did not occur at 1,600 mcg/kg in the other study. In addition, no increase in the number of resorptions was seen in two rat teratology studies at dosage levels up to 10,000 mcg/kg. The increased number of resorptions and decreased number of implantations accounted for a decreased number of live fetuses or pups at 10,000 mcg/kg. The decreased number of implantations accounted for a decreased number of fetuses at 1,600 mcg/kg compared to a control group, although values remained within the historical control range for the strain. Fetal and pup survival or growth were unaffected. Behavioral, sensory, and reproductive assessment of the F_1 offspring revealed no adverse effects.

There was no evidence of embryotoxicity, fetotoxicity, or teratogenicity in two teratology rat studies at the maximum dosage of 10,000 mcg/kg.

No evidence of fetotoxicity or teratogenicity was observed in two teratology rabbit studies at the maximum dosage of 1,000 mcg/kg. However, there was an increased number of resorptions, evidence of possible embryotoxicity, in one of the two studies at 1,000 mcg/kg.

In the perinatal/postnatal study, pup growth at 10,000 mcg/kg was retarded as evidenced by the decreased weight gain during lactation. However, pup survival was unaffected.

Mutagenicity Studies

The mutagenic/carcinogenic potential of misoprostol was evaluated in seven *in vitro* tests and one *in vivo* test: Ames Salmonella/microsome assay; mouse lymphoma $TK^{+/-}$ assay; sister chromatid exchange assay; yeast gene conversion assay; and the C_3H 10T1/2 cell transformation assay; reverse mutation study using E. coli; chromosomal aberration assay; and micronucleus assay with misoprostol dispersion. Misoprostol was negative in all tests. Ames tests were also negative for misoprostol degradation products (SC-29636, SC-32759, SC-33188).

Carcinogenicity Studies

Carcinogenicity studies were conducted in rats and mice.

Rats: Misoprostol was administered by gavage once daily for 104 to 106 weeks to Charles River CD rats (60 animals/sex/dosage group) at dosages of 24, 240 and 2,400 mcg/kg. Two water control and one HPMC control groups were included. Mortality was similar between groups and deaths were not considered to be related to drug treatment. Treatment-related signs were soft feces and loose stools at 2,400 mcg/kg and sporadically at 240 mcg/kg, increased salivation at 2,400 mcg/kg and dilated vaginal opening at a very low incidence at 2,400 mcg/kg. Other signs observed during the study were considered to be incidental. The mean body weights for the animals of both sexes of the 2,400 mcg/kg group were significantly lower than those of the pooled water control groups (about 22% at the end of the study). For the males of the 240 mcg/kg group, the mean body weight was about 7% lower than that of the pooled water control males at the end of the study.

All neoplasms, both benign and malignant, in control and treated rats were types commonly found in old rats of the strain used. No neoplasms occurred unusually early nor were there any unusual

types. Misoprostol did not cause an increase in frequency of any tumor. There was no evidence of any dysplastic or preneoplastic change in gastrointestinal epithelial cells nor were there any neoplasms of the gastrointestinal mucosa. The expected hyperplasia of gastric squamous and surface mucus cells and colonic epithelial cells occurred mainly at 240 and 2,400 mcg/kg. The gastric effect was seen both grossly and microscopically, whereas the colonic effect was seen only microscopically in a few rats at 2,400 mcg/kg. The mean weight of the stomachs and stomach to body weight ratios showed the expected increases with increasing dosage of misoprostol.

It was concluded from this study that misoprostol is not carcinogenic in rats.

Mice: Misoprostol was given by gavage once daily for 91 to 94 weeks to Charles River CD-1 mice (64/sex/dosage group) at dosages of 160, 1,600 and 16,000 mcg/kg). Two water control and one HPMC control groups were included. Mortality at 16,000 mcg/kg was slightly higher than in other groups. Treatment-related signs of soft feces and loose stools were observed at 16,000 mcg/kg and sporadically at 1,600 mcg/kg. Abdominal distension occurred in all groups after 16 months but with a higher incidence in the 16,000 mcg/kg group. Other signs were regarded as incidental. The mean body weights and food consumption for female mice of the 16,000 mcg/kg group were significantly higher than those of the pooled water control groups.

All neoplasms, both benign and malignant, in control and treated mice, were types commonly seen in old mice. There was no evidence of an association between any tumor and administration of misoprostol.

The expected proliferative effect of misoprostol on gastric squamous and surface mucus cells occurred mainly in mice of the 1,600 and 16,000 mcg/kg dosage groups. Slight epithelial hyperplasia was noted microscopically in the large intestine of a few 16,000 mcg/kg group mice.

Focal avillous hyperplasia and junctional polyp, which are unique to the duodenum of the mouse, occurred mainly in 16,000 mcg/kg group animals. This apparent relationship to misoprostol is considered to be nonspecific since both lesions occur spontaneously.

Medullary hyperostosis of the sternum and femur occurred in a large number of female mice of the 1,600 and 16,000 mcg/kg groups and in a few male mice of the 16,000 mcg/kg group only. Although there is a relationship to administration of misoprostol, the high incidence in female mice may be related to an additional factor, estrogen. Evidence of estrogenic activity was shown by a high incidence of cystic ovaries and cystic endometrial hyperplasia. The mouse is unique among mammals in responding to estrogen by developing medullary hyperostosis.

It was concluded from this study that misoprostol is not carcinogenic in mice.

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