Summary Basis of Approval

NDA 19-268

Applicant:
G.D. Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

Drug Generic Name:
Misoprostol

Drug Trade Name:
Cytotec

I. Indication for Use

Cytotec (misoprostol) is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin) induced gastric ulcers in patients at high risk of complications from a gastric ulcer, eg, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Cytotec has not been shown to prevent duodenal ulcers in patients taking NSAIDs. Cytotec should be taken for the duration of NSAID therapy. Cytotec has been shown to prevent gastric ulcers in controlled studies of three months duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

II. Dosage Form(s), Route(s) of Administration and Recommended Dosages

A. Dosage Form(s) and Route(s) of Administration

Misoprostol 200 mcg tablets for oral administration are white, hexagonal, with SEARLE debossed above and 1461 debossed below the line on one side and a double stomach debossed on the other side; supplied as bottles of 100 tablets (NDC 0025-1461-31) and cartons of 100 unit-dose tablets (NDC 0025-1461-34).

B. Recommended Dosages

The recommended adult oral dosage of misoprostol for the prevention of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg Q.I.D. can be used. Misoprostol should be taken for the duration of NSAID therapy as prescribed by the physician.

Misoprostol should be taken with a meal, and the last dose should be taken at bedtime.

III. Manufacturing and Controls

A. Manufacturing and Control's

The new drug substance is synthesized by a convergent multistep organic procedure. The specifications for the new drug substance and the methods used to test these specifications are adequate to assure the identity, strength, quality, and purity of the bulk drug.

The tablets are manufactured in compliance with CGMPs. Acceptance tests and specifications for the inactive ingredients are adequate. Tests, methods and specifications for the finished tablets are adequate to establish and maintain the identity, strength, quality and purity of the drug product.

B. Stability

Sufficient long term and accelerated stability data on 2 lots of tablets in HDPE plastic containers with metal closures and 2 additional lots in blisterpak warrant the following expiration dating:

HDPE bottles	18 months
Blisterpak	18 months

C. Methods Validation

The methods validation has been evaluated by two FDA laboratories, and has been deemed acceptable for regulatory purposes.

D. Labeling

The immediate container labels and the Description and How Supplied sections of the package insert conform to current regulations.

Insofar as could be determined from a thorough search of available references, the trade name Cytotec is not in conflict with the name of any other drug.

E. Establishment Inspection

Manufacturing Review Branch has concluded that there is no reason to withhold approval of this application.

F. Environmental Impact Analysis Report (EIAR)

A report has been provided. It has been reviewed and is considered acceptable.

IV. Pharmacology

A. Pharmacodynamics

Misoprostol is an orally active synthetic analog of Prostaglandin E for the reduction of histamine, gastrin or meal stimulated gastric acid secretion. It also protects against gastrointestinal lesions induced by various agents in laboratory animals.

1. Gastric Antisecretory Studies

In the dog, misoprostol inhibited histamine-, pentagastrin-, and meal-stimulated gastric acid secretion. Maximal inhibition of total acid output was approximately 95% with a 3.0 mcg/kg intravenous dose given to Heidenhain pouch dogs after meal stimulation.

In dogs with innervated (Pavlov) pouches, misoprostol decreased total acid output by reduction of both volume and acid concentration. The greatest antisecretory activity occurred when misoprostol was allowed to come into direct contact with the secreting surface of gastric epithelial tissue, indicating that misoprostol is absorbed from the stomach lumen directly into the gastric mucosa.

Intragastric administration of misoprostol decreased the gastric acid concentration in pylorus ligated rats (ED_{50}=30 mcg/kg).

In isolated rabbit gastric glands, misoprostol reduced histamine-stimulated ^{14}C-aminopyrine accumulation, a marker for acid secretion, in a dose-dependent fashion. In vitro studies on canine parietal cells with tritiated misoprostol acid as ligand led to the identification and characterization of specific prostaglandin receptors. These receptors are located on the surface of the parietal cell and number approximately 8,000 per cell. The sites have a high affinity for misoprostol, for its acid metabolite and for other prostaglandins of the E type, but not for F or I prostaglandins or for other unrelated compounds such as histamine or cimetidine. Receptor site affinity for misoprostol correlates well with an indirect index of antisecretory activity.

2 Gastric Mucosal Blood Flow Studies

Gastric mucosal blood flow was estimated by ^{14}C-aminopyrine clearance in dogs surgically prepared with Heidenhain pouches. Gastric acid secretion was stimulated by histamine infusion. Results indicated that misoprostol did not inhibit gastric acid secretion secondarily to diminished gastric mucosal blood flow.

Mucosal blood flow in the gastric corpus was also measured by hydrogen gas clearance in fasted anesthetized rats both in the basal state and after pentagastrin stimulation. The results showed that misoprostol had no effect on basal gastric corpus mucosal blood flow, and that during pentagastrin stimulation, misoprostol significantly decreased acid secretion but did not decrease mucosal blood flow.

3. Duodenal Bicarbonate Secretion

Graded doses of misoprostol were examined for effects on duodenal bicarbonate output in fasted conscious rats. Chronic loops of proximal duodenum were prepared, the loops were perfused with isotonic saline, and samples of 15-minute effluent were analyzed for bicarbonate content. Misoprostol, added to the perfusate, produced a dose-dependent increase in bicarbonate secretion.

4. Gastric Mucus Secretion

Luminal and adherent mucus were measured in fasted rats which were untreated or had received doses of misoprostol 50 mcg/kg, 100 mcg/kg, or 1,000 mcg/kg. Misoprostol at doses of 100 mcg/kg and 1,000 mcg/kg produced a marked rise in luminal mucous glycoprotein and a significant increase in the median thickness of adherent mucous gel one hour after administration.

5. Gastric and Duodenal Antiulcer Studies

Intragastric misoprostol at 10 mcg/kg provided significant protection against ethanol-induced gastric lesion formation in the rat. Oral administration of 30 mcg/kg misoprostol produced a significant reduction in the number of taurocholic acid-induced gastric lesions and in gastric lesions using the pyloric ligation technique. Lesion formation was reduced by subcutaneous misoprostol administration at 300 mcg/kg in the forced exertion stress rat gastric ulcer model.

In the guinea pig histamine-induced duodenal ulcer model, misoprostol decreased ulcer score with 10 mcg/kg doses administered b.i.d. for 2 days subcutaneously.

In cats, a gastrin pentapeptide infusion was used to produce duodenal ulcers. The simultaneous infusion of misoprostol at 0.5 mcg/kg/hr reduced ulcer formation.