MISOPROSTOL (Systemic)

Category

Gastric mucosa protectant; antiulcer agent.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Ulcer, gastric, nonsteroidal anti-inflammatory drug-induced (prophylaxis)¾Misoprostol is indicated for the prevention of gastric ulcer associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, in patients at high risk of complications from gastric ulcer, such as the elderly, and in patients with concomitant disease or patients at high risk of developing gastric ulceration, such as those with a history of ulcer. 1, 5, 6, 7, 10, 14, 17, 20

[Ulcer, gastric, nonsteroidal anti-inflammatory drug-induced (treatment)]¾Misoprostol is indicated for the treatment of gastric ulcer associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

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[Ulcer, duodenal (treatment)]¾Misoprostol is indicated in the short-term treatment of duodenal ulcer caused by peptic ulcer disease (PUD). 3, 10, 12, 20

Acceptance not established

Some studies have suggested the use of misoprostol as an alternative agent in the prevention of postpartum hemorrhage, especially in the developing countries. However, there are insufficient data to establish its efficacy for this indication and, therefore, further studies are warranted. 19

Pharmacology

Mechanism of action/Effect:

Cytoprotective¾Misoprostol enhances natural gastromucosal defense mechanisms and healing in acid-related disorders, probably by increasing production of gastric mucus and mucosal secretion of bicarbonate. 1, 8, 9, 10

Antisecretory¾Misoprostol inhibits basal and nocturnal gastric acid secretion by direct action on the parietal cells; also inhibits gastric acid secretion stimulated by food, coffee, histamine, and pentagastrin. It decreases pepsin secretion under basal, but not histamine, stimulation. Misoprostol has no significant effect on fasting or postprandial gastrin or intrinsic factor output. 1, 17

Other actions/effects:

Misoprostol may produce uterine contractions, bleeding, and expulsion of the products of conception. 17

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to other prostaglandins or prostaglandin analogs may be sensitive to misoprostol also. 17

Carcinogenicity/Mutagenicity

Animal studies have not shown misoprostol to be carcinogenic or mutagenic. 1, 12, 17

Pregnancy/Reproduction

Pregnancy¾Misoprostol is contraindicated during pregnancy. Studies in humans have shown that misoprostol causes an increase in the frequency and intensity of uterine contractions. Misoprostol administration also has been associated with a higher incidence of uterine bleeding and expulsion of uterine contents. Miscarriages caused by misoprostol are likely to be incomplete, resulting in very serious medical complications, sometimes requiring hospitalization and surgery, and possibly causing infertility 1, 17.

FDA Pregnancy Category X. 17

Patients of childbearing potential may use misoprostol if nonsteroidal anti-inflammatory drug (NSAID) therapy is required and patient is at high risk of complications from gastric ulcers associated with the use of NSAIDs, or is at high risk of developing gastric ulceration. Such patients must comply with effective contraceptive measures, must have had a negative serum pregnancy test within 2 weeks prior to initiation of therapy, and must start misoprostol therapy only on the second or third day of the next normal menstrual period. 1, 17

Breast-feeding

It is unlikely that misoprostol is distributed into breast milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite, misoprostol acid, is distributed into breast milk. Therefore, administration of misoprostol to nursing women is not recommended because of the potential distribution of misoprostol acid, which could cause significant diarrhea in the nursing infant. 1, 10, 17

Pediatrics

Appropriate studies on the relationship of age to the effects of misoprostol have not been performed in patients up to 18 years of age. 10 Safety and efficacy have not been established. 12, 17

Geriatrics

Studies performed in approximately 500 ulcer patients 65 years of age or older have not demonstrated geriatrics-specific problems that would limit the usefulness of misoprostol in the elderly. 1, 17

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Magnesium-containing antacids

(concurrent use with misoprostol may aggravate misoprostol-induced diarrhea 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

Cerebral vascular disease 1, 12 or

Coronary artery disease 1, 12

(although the effect has not been reported with misoprostol, prostaglandins and prostaglandin analogs have been reported to cause hypotension via peripheral vasodilation, thus increasing the risk of severe complications in these conditions)

Epilepsy 1, 10, 12

(although the effect has not been reported with misoprostol, prostaglandins and prostaglandin analogs have been reported to cause epileptic seizures when given by routes other than oral; it is recommended that misoprostol be used in epileptics only when their condition is adequately controlled)

Inflammatory bowel disease 17

(diarrhea may be exacerbated, leading to dehydration; careful monitoring is recommended)

Sensitivity to prostaglandins or prostaglandin analogs 10

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal or stomach pain, mild 1; diarrhea 1

Note: Diarrhea is dose-related. It usually develops early in the course of therapy and is self-limiting, often resolving after 8 days. However, rare instances of profound diarrhea leading to severe dehydration have been reported, and some patients have required discontinuation of misoprostol because of continuing severe diarrhea. 1, 12, 17

Incidence less frequent or rare 1

Constipation 12, 17;

dyspepsia 17 (heartburn, indigestion, or acid stomach); flatulence 17 (gas); headache 12, 17; nausea and/or vomiting 12, 17; uterine stimulation 1 (cramps in lower abdomen or stomach area); vaginal bleeding 1

Overdose

The toxic dose in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated with only gastrointestinal disturbances. 17

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Abdominal pain 17; bradycardia 17 (slow heartbeat); diarrhea 17; dyspnea 17 (troubled breathing); fever 17; hypotension 17 (low blood pressure); palpitations 17 (fast or pounding heartbeat); sedation 17 (drowsiness); seizures 17; tremor 17
Treatment of overdose

There is no specific treatment for misoprostol overdose. Treatment should be symptomatic, and general supportive care is indicated.Elimination¾It is not known if misoprostol acid is dialyzable. However, misoprostol is metabolized like a fatty acid, so it is unlikely that dialysis would be appropriate treatment for overdosage. 17

Supportive care¾Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Misoprostol (Systemic) .In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to prostaglandins or prostaglandin analogs
Pregnancy¾Contraindicated during pregnancy because of risk of miscarriage; patients of childbearing potential must take measures to assure they are not pregnant prior to therapy and to prevent pregnancy during therapy
Breast-feeding¾Not recommended because of possibility of causing diarrhea in nursing infant
Proper use of this medication

Taking with or after meals and at bedtime

>> Proper dosing
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

>> Stopping medication and checking with physician immediately if pregnancy is suspected

Consulting physician if diarrhea develops and continues for more than a week

Side/adverse effects

Signs of potential side effects, especially continuing and severe diarrhea, stomach pain, constipation, dyspepsia, flatulence, headache, nausea and/or vomiting, uterine stimulation, vaginal bleeding

General Dosing Information

Misoprostol therapy should be started at the onset of treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), and continued for the duration of NSAID therapy. 1

Misoprostol should be taken with or after meals and at bedtime, for maximum effectiveness. 1, 10 Taking with food or milk will lessen adverse effects such as loose stools, diarrhea, and abdominal cramping. 12

If required, antacids may be administered before or after misoprostol for the relief of pain. However, magnesium-containing antacids are not recommended since they may aggravate misoprostol-induced diarrhea. 1, 12

Misoprostol has not been shown to have an effect on gastrointestinal pain or discomfort 12, 17 ; caution should be used when relying on symptomatology as the sole diagnostic and follow-up procedure. 12

For treatment of duodenal ulcer

Therapy with misoprostol should continue for a total of 4 weeks unless healing has been documented by endoscopic examination. If necessary, treatment may continue for an additional 4 weeks if ulcers have not fully healed after the initial 4 weeks. 10, 12

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

MISOPROSTOL TABLETS

Usual adult dose

Prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcer¾Oral, 200 mcg (0.2 mg) four times a day with food 17 or 400 mcg (0.4 mg) two times a day with food. 10

[Treatment of nonsteroidal anti-inflammatory drug-induced gastric ulcer]¾Oral, 400 mcg (0.4 mg) to 800 mcg (0.8 mg) a day in divided doses, taken immediately after a meal or with food or milk. When appropriate should be taken simultaneously with nonsteroidal anti-inflammatory drugs (NSAIDs). 20

[Treatment of duodenal ulcer]¾Oral, 800 mcg (0.8 mg) a day in two or four divided doses (200 mcg four times a day or 400 mcg two times a day), for four weeks, taken with food. If necessary, treatment may be continued for additional four weeks if ulcers have not fully healed after the initial four-week treatment. 20

Note: The last dose of the day should be taken at bedtime 10, 17 with food. 20

Dose may be reduced to 100 mcg (0.1 mg) in those patients sensitive to higher doses. 1

Patients with renal impairment do not routinely require dosage adjustments. However, in patients with renal failure, a starting dose of 100 mcg (0.1 mg) is recommended 12, 20.

Usual pediatric and adolescent dose

Dosage has not been established.

Usual geriatric dose

See Usual adult dose.

Note: Dosage may need to be reduced if usual dose is not tolerated. 20

Strength(s) usually available

U.S.¾0.1 mg (Rx)[Cytotec (scored)]

0.2 mg (Rx)[Cytotec (scored)]

Canada¾0.1 mg (Rx)[Cytotec]

0.2 mg (Rx)[Cytotec (scored)]

Note: Dispense with patient insert. 20

Packaging and storage:

Store at or below 25 °C (77 °F), in a well-closed container, unless otherwise specified by manufacturer. Protect from light, moisture and humidity. 20

Auxiliary labeling:

· Take with food or milk.
· Continue medicine for full time of treatment.
· Do not give medication to any other persons. 1, 12

References

1 Cytotec package insert (Searle¾US), Rev 4/91, Rec 1/92.

2 Tierney M. Misoprostol: a synthetic prostaglandin derivative for peptic ulcer disease. Can Pharm J 1987; 440-3.

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5 Cohen M, Clark L, Armstrong L, D"Souza J. Reduction of aspirin-induced fecal blood loss with low-dose misoprostol tablets in man. Dig Dis Sci 1985; 30: 605-11.

6 Hunt J, Smith J, Jiang C, Kessler L. Effect of synthetic prostaglandin E 1 analog on aspirin-induced gastric bleeding and secretion. Dig Dis Sci 1983; 28: 897-902.

7 Lanza F. Prophylatic effect of misoprostol on lesions of the gastric mucosa induced by oral administration of tolmetin in healthy subjects. Abstract from 2nd International Symposium, New York City, May 1985: 54.

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9 Selling J, Hogan D, Kass M, Isenberg J. Prostaglandin E 1 (misoprostol) stimulates human duodenal mucosal bicarbonate secretion. Am J Gastroenterol 1985; 88(Pt 2): 1580.

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14 Agrawal N, Roth S, Graham D, White R, Germain B, Brown J. Misoprostil compared with sucralfate in the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcer. Ann Intern Med 1991; 115(3): 195-200.

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17 Cytotec package insert (Searle¾US), Rev 8/8/95, Rec 3/16/99.

18 Canada JR, editor. USP dictionary of USAN and international drug names 1998. Rockville, MD: The United States Pharmacopeial Convention Inc; 1997. p. 479.

19 Reviewers consensus. 5/2000.

20 Product Information: Cytotec, misoprostol. Searle Canada, Missasauga, Ontario, (PI Revised 05/2000) PI Reviewed 01/2001.