DICLOFENAC SODIUM AND MISOPROSTOL- diclofenac sodium and misoprostol tablet, film coated
Greenstone LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use diclofenac sodium/misoprostol safely and effectively. See full prescribing information for diclofenac sodium/misoprostol.

Diclofenac sodium/misoprostol delayed-release tablets, for oral use
Initial U.S. Approval:1997

WARNING: RISK OF UTERINE RUPTURE, ABORTION, PREMATURE BIRTH, BIRTH DEFECTS; SERIOUS CARDIOVASCULAR EVENTS; AND SERIOUS GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- **Administration of misoprostol, a component of diclofenac sodium/misoprostol, to pregnant women can cause uterine rupture, abortion, premature birth, or birth defects. Uterine rupture has occurred when misoprostol was administered in pregnant women to induce labor or an abortion. (4, 5.1, 8.1)**
- **Diclofenac sodium/misoprostol is contraindicated in pregnancy and is not recommended in women of childbearing potential. Patients must be advised of the abortifacient property and warned not to give the drug to others. (5.1, 8.3)**
- **Increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. (5.2)**
- **Diclofenac sodium/misoprostol is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.2)**
- **Increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal and can occur at any time and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk. (5.3)**

INDICATIONS AND USAGE

Diclofenac sodium/misoprostol is a combination of diclofenac sodium, a non-steroidal anti-inflammatory drug, and misoprostol, a prostaglandin-1 (PGE1) analog, indicated for the treatment of signs and symptoms of osteoarthritis or rheumatoid arthritis in adult patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. (1)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Osteoarthritis: The recommended dosage for maximal GI protection is one tablet (containing 50 mg of diclofenac and 200 mcg of misoprostol) three times daily. A dosage of diclofenac higher than 150 mg/day is not recommended. (2.2)
- Rheumatoid Arthritis: The recommended dosage for maximal GI protection is one tablet (containing 50 mg of diclofenac and 200 mcg of misoprostol) three or four times daily A dosage of diclofenac higher than 200 mg/day is not recommended. (2.3)
- For dosage modifications due to intolerance, see the full Prescribing Information. (2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

Delayed-release tablets:

- 50 mg diclofenac sodium and 200 mcg misoprostol (3)
- 75 mg diclofenac sodium and 200 mcg misoprostol (3)

CONTRAINDICATIONS

- Pregnancy (4)
- In the setting of CABG surgery (4)
- Active gastrointestinal bleeding (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- Known hypersensitivity to diclofenac sodium, misoprostol, or any components of the drug product (4)

WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity with NSAIDs: Use of NSAIDs, including diclofenac in women at about 20 weeks gestation and later in pregnancy may cause oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus. (4, 5.1, 8.1)
- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.4)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.5, 7)
- Heart Failure and Edema: Avoid in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. (5.6)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function. (5.7)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs. (5.8)
- Exacerbation of Asthma Related to Aspirin Sensitivity: Contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.9)
- Serious Skin Reactions: Discontinue at first appearance of skin rash or other signs of hypersensitivity. (5.10)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically. (5.11)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.12, 7)

ADVERSE REACTIONS

Most common adverse reactions (>2%) are: abdominal pain, diarrhea, dyspepsia, nausea, flatulence, gastritis, vomiting, constipation, headache, dizziness, alanine aminotransferase increased, hematocrit decreased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See full prescribing information for a list of clinically important drug interactions. (7)

USE IN SPECIFIC POPULATIONS

- Reversible Infertility: Consider withdrawal in women who have difficulties conceiving. (8.3)
- Geriatric Patients: Avoid use in patients with cardiovascular and/or renal risk factors. (8.5)
- Renal Impairment: Avoid use in patients with advanced renal disease. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF UTERINE RUPTURE, ABORTION, PREMATURE BIRTH, BIRTH DEFECTS; SERIOUS CARDIOVASCULAR EVENTS; AND SERIOUS GASTROINTESTINAL EVENTS

Uterine Rupture, Abortion, Premature Birth, and Birth Defects

- **Administration of misoprostol, a component of diclofenac sodium/misoprostol, to pregnant women can cause uterine rupture, abortion, premature birth, or birth defects. Uterine rupture has occurred when misoprostol was administered in pregnant women to induce labor or an abortion *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.**
- **Diclofenac sodium/misoprostol is contraindicated in pregnancy *[see Contraindications (4)]* and not recommended in women of childbearing potential. Patients must be advised of the abortifacient property and warned not to give the drug to others *[see Warnings and Precautions (5.1)]*.**
- **If diclofenac sodium/misoprostol is prescribed, verify the pregnancy status of females of reproductive potential prior to initiation of treatment and advise them to use effective contraception during treatment *[see Use in Specific Populations (8.3)]*.**

Cardiovascular Thrombotic Events

- **NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use *[see Warnings and Precautions (5.2)]*.**
- **Diclofenac sodium/misoprostol is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4) and Warnings and Precautions (5.2)]*.**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

Diclofenac sodium/misoprostol is indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in adult patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. For a list of factors that may increase the risk of NSAID-induced gastric and duodenal ulcers and their complications *[see Warnings and Precautions (5.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- Carefully consider the potential benefits and risks of diclofenac sodium/misoprostol and other treatment options before deciding to use diclofenac sodium/misoprostol. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)].*
- After observing the response to initial therapy with diclofenac sodium/misoprostol, the dose and frequency should be adjusted to suit an individual patient's needs.
- Diclofenac sodium/misoprostol is not recommended for patients who would not receive the appropriate dosage of both active ingredients.
- Diclofenac sodium/misoprostol, a fixed combination product, is administered as diclofenac sodium/misoprostol 50 (50 mg diclofenac sodium and 200 mcg misoprostol) or as diclofenac sodium/misoprostol 75 (75 mg diclofenac sodium and 200 mcg misoprostol).

2.2 Recommended Dosage in Patients with Osteoarthritis

The recommended dosage for the treatment of osteoarthritis for maximal GI mucosal protection is diclofenac sodium/misoprostol 50 three times a day. For patients who experience intolerance, diclofenac sodium/misoprostol 75 two times a day or diclofenac sodium/misoprostol 50 two times a day can be used, but these dosages are less effective in preventing ulcers. A daily dosage of diclofenac sodium greater than 150 mg/day is not recommended. Daily doses of the components delivered with these regimens are as follows:

	Osteoarthritis Regimen	**Diclofenac sodium (mg/day)**	**Misoprostol (mcg/day)**
Diclofenac sodium/misoprostol 50	three times a day	150	600
	two times a day*	100	400
Diclofenac sodium/misoprostol 75	two times a day*	150	400

* For patients who experience intolerance; these dosages are less effective in preventing ulcers

2.3 Recommended Dosage in Patients with Rheumatoid Arthritis

The recommended dosage for the treatment of rheumatoid arthritis is diclofenac sodium/misoprostol 50 three or four times a day. For patients who experience intolerance, diclofenac sodium/misoprostol 75 two times a day or diclofenac sodium/misoprostol 50 two times a day can be used, but are less effective in preventing ulcers. A daily dosage of diclofenac sodium greater than 200 mg/day is not recommended. Daily doses of the components delivered with these regimens are as follows:

	Rheumatoid Arthritis Regimen	**Diclofenac sodium (mg/day)**	**Misoprostol (mcg/day)**

Diclofenac sodium/misoprostol 50	four times a day	200	800
	three times a day	150	600
	two times a day*	100	400
Diclofenac sodium/misoprostol 75	two times a day*	150	400

* For patients who experience intolerance; these dosages are less effective in preventing ulcers

2.4 Additional Dosage Recommendations

Diclofenac sodium/misoprostol contains misoprostol, which provides protection against gastric and duodenal ulcers *[see Clinical Studies (14)]*. For gastric ulcer prevention, the 200 mcg four and three times a day regimens are therapeutically equivalent, but more protective than the two times a day regimen. For duodenal ulcer prevention, the four times a day regimen is more protective than the three or two times a day regimens. However, the four times a day regimen is less well tolerated than the three times a day regimen because of usually self-limited diarrhea related to the misoprostol dose *[see Adverse Reactions (6.1)]*, and the two times a day regimen may be better tolerated than three times a day in some patients.

Dosages may be individualized using the separate products (misoprostol and diclofenac sodium), after which the patient may be switched to the appropriate diclofenac sodium/misoprostol dosage. If clinically indicated, misoprostol co-therapy with diclofenac sodium/misoprostol to optimize the misoprostol dose and/or frequency of administration, may be appropriate. Do not exceed a total misoprostol dose of 800 mcg/day and do not administer more than 200 mcg of misoprostol at any one time.

When concomitant use of CYP2C9 inhibitors is necessary, the maximum total daily dose of diclofenac is 100 mg per day. Do not exceed a dosage of diclofenac sodium/misoprostol 50 mg twice daily *[see Drug Interactions (7)]*.

For additional information, refer to the Prescribing Information for the individual products of diclofenac sodium and misoprostol.

3 DOSAGE FORMS AND STRENGTHS

Delayed-release tablets:

- 50 mg diclofenac sodium and 200 mcg misoprostol as round, biconvex, white to off-white tablets imprinted with a “50” in the middle on one side and “G” and “0028” on the other.
- 75 mg diclofenac sodium and 200 mcg misoprostol as round, biconvex, white to off-white tablets imprinted with a “75” in the middle on one side and “G” and “0029” on the other.

4 CONTRAINDICATIONS

Diclofenac sodium/misoprostol is contraindicated in the following patients:

- Pregnancy. Use of misoprostol, a component of diclofenac sodium/misoprostol, during pregnancy can result in maternal and fetal harm, including uterine rupture,

abortion, premature birth, or birth defects *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*
- In the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.2)]*
- Active gastrointestinal bleeding *[see Warnings and Precautions (5.3)]*
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (5.8, 5.9)]*
- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac sodium and misoprostol, other prostaglandins, or any components of the drug product *[see Warnings and Precautions (5.8, 5.10)]*

5 WARNINGS AND PRECAUTIONS

5.1 Uterine Rupture, Abortion, Premature Birth, or Birth Defects with Misoprostol and Embryo-Fetal Toxicity with NSAIDs

Misoprostol

Administration of misoprostol, a component of diclofenac sodium/misoprostol, to pregnant women can cause uterine rupture, abortion, premature birth, or birth defects. Uterine rupture has occurred when misoprostol was administered to pregnant women to induce labor or an abortion.

Diclofenac sodium/misoprostol is contraindicated in pregnant women. Diclofenac sodium/misoprostol is not recommended in women of childbearing potential. Patients must be advised of the abortifacient property and warned not to give the drug to others *[see Use in Specific Populations (8.1)]*.

If diclofenac sodium/misoprostol is prescribed, verify the pregnancy status of females of reproductive potential prior to initiation of treatment and advise the use effective contraception during treatment with diclofenac sodium/misoprostol *[see Use in Specific Populations (8.3)]*.

Diclofenac

Premature Closure of Fetal Ductus Arteriosus

NSAIDs, including diclofenac, a component of diclofenac sodium/misoprostol, increase the risk of premature closure of the fetal ductus arteriosus at about 30 weeks of gestation and later.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including diclofenac, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange

transfusion or dialysis were required *[see Use in Specific Populations (8.1)]*.

5.2 Cardiovascular Thrombotic Events

Clinical trials of several cyclooxygenase-2 (COX-2) selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as diclofenac, increases the risk of serious gastrointestinal (GI) events *[see Warnings and Precautions (5.3)]*.

<u>Status Post Coronary Artery Bypass Graft (CABG) Surgery</u>

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *[see Contraindications (4)]*.

<u>Post-MI Patients</u>

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of diclofenac sodium/misoprostol in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If diclofenac sodium/misoprostol is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.3 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including diclofenac, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach,

small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue diclofenac sodium/misoprostol until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *[see Drug Interactions (7)]*.

5.4 Hepatotoxicity

In clinical trials with diclofenac sodium/misoprostol, meaningful elevation of alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT], more than 3 times the upper limit of the normal range [ULN]) occurred in 1.6% of 2,184 patients treated with diclofenac sodium/misoprostol and in 1.4% of 1,691 patients treated with diclofenac sodium. These increases were generally transient, and enzyme levels returned to within the normal range upon discontinuation of therapy with diclofenac sodium/misoprostol. The misoprostol component of diclofenac sodium/misoprostol does not appear to exacerbate the hepatic effects caused by the diclofenac sodium component.

In clinical trials of diclofenac-containing products, meaningful elevations (i.e., more than 3 times the ULN) of aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT]) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment (ALT was not measured in all studies).

In a large, open-label, controlled trial of 3,700 patients treated with oral diclofenac sodium for 2 to 6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in

about 4% of patients and included marked elevations (i.e., greater than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3 to 8 times the ULN), and marked (greater than 8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

In a European retrospective population-based, case-controlled study, 10 cases of diclofenac associated drug-induced liver injury with current use compared with non-use of diclofenac were associated with a statistically significant 4-fold adjusted odds ratio of liver injury. In this particular study, based on an overall number of 10 cases of liver injury associated with diclofenac, the adjusted odds ratio increased further with female gender, doses of 150 mg or more, and duration of use for more than 90 days.

Physicians should measure transaminases at baseline and periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), diclofenac sodium/misoprostol should be discontinued immediately.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue diclofenac sodium/misoprostol immediately, and perform a clinical evaluation of the patient.

To minimize the potential risk for an adverse liver related event in patients treated with diclofenac sodium/misoprostol, the lowest effective dose should be used for the shortest duration possible. Exercise caution when prescribing diclofenac sodium/misoprostol with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

5.5 Hypertension

NSAIDs, including diclofenac, a component of diclofenac sodium/misoprostol, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs *[see Drug Interactions (7)]*.

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.6 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of diclofenac may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) *[see Drug Interactions (7)]*.

Avoid the use of diclofenac sodium/misoprostol in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If diclofenac sodium/misoprostol is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.7 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of diclofenac sodium/misoprostol in patients with advanced renal disease. The renal effects of diclofenac sodium/misoprostol may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating diclofenac sodium/misoprostol. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of diclofenac sodium/misoprostol *[see Drug Interactions (7)].* Avoid the use of diclofenac sodium/misoprostol in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If diclofenac sodium/misoprostol is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.8 Anaphylactic Reactions

Diclofenac sodium/misoprostol has been associated with anaphylactic reactions in patients with and without known hypersensitivity to the individual components of diclofenac sodium and misoprostol and in patients with aspirin-sensitive asthma *[see Contraindications (4) and Warnings and Precautions (5.9)]*.

Seek emergency help if an anaphylactic reaction occurs.

5.9 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, diclofenac sodium/misoprostol is contraindicated in patients with this form of aspirin sensitivity *[see Contraindications (4)]*. When diclofenac sodium/misoprostol is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.10 Serious Skin Reactions

NSAIDs, including diclofenac, a component of diclofenac sodium/misoprostol, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of diclofenac sodium/misoprostol at the first appearance of skin rash or any other sign of hypersensitivity. Diclofenac sodium/misoprostol is contraindicated in patients with previous serious skin reactions to NSAIDs *[see Contraindications (4)]*.

5.11 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as diclofenac sodium/misoprostol. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue diclofenac sodium/misoprostol and evaluate the patient immediately.

5.12 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with diclofenac sodium/misoprostol has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including diclofenac, a component of diclofenac sodium/misoprostol, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin and other anticoagulants, antiplatelet drugs (e.g., aspirin), and SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding *[see Drug Interactions (7)]*.

5.13 Masking of Inflammation and Fever

The pharmacological activity of diclofenac, a component of diclofenac sodium/misoprostol, in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a complete blood count (CBC) and a chemistry profile periodically *[see Warnings and Precautions (5.3, 5.7)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.2)]*
- GI Bleeding, Ulceration and Perforation *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Hypertension *[see Warnings and Precautions (5.5)]*
- Heart Failure and Edema *[see Warnings and Precautions (5.6)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.7)]*
- Anaphylactic Reactions *[see Warnings and Precautions (5.8)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.10)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reaction information for diclofenac sodium/misoprostol is derived from multinational controlled clinical trials in over 2,000 patients receiving diclofenac sodium/misoprostol 50 or diclofenac sodium/misoprostol 75, as well as from blinded, controlled trials of diclofenac sodium delayed-release tablets and misoprostol tablets

<u>Gastrointestinal</u>

GI disorders had the highest reported incidence of adverse reactions for patients receiving diclofenac sodium/misoprostol. These events were generally minor, but led to discontinuation of therapy in 9% of patients on diclofenac sodium/misoprostol and 5% of patients on diclofenac sodium. For GI ulcer rates, *[see Clinical Studies (14)].*

GI disorder	**Diclofenac sodium/misoprostol**	**Diclofenac Sodium**
Abdominal pain	21%	15%
Diarrhea	19%	11%
Dyspepsia	14%	11%
Nausea	11%	6%
Flatulence	9%	4%

Diclofenac sodium/misoprostol can cause more abdominal pain, diarrhea, and other GI symptoms than diclofenac alone.

Diarrhea and abdominal pain developed early in the course of therapy, and were usually self-limited (resolved after 2 to 7 days). Rare instances of profound diarrhea leading to severe dehydration have been reported in patients receiving misoprostol. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if diclofenac sodium/misoprostol is prescribed. The incidence of diarrhea can be minimized by administering diclofenac sodium/misoprostol with food and by avoiding coadministration with magnesium-containing antacids.

Gynecological

Gynecological disorders previously reported with misoprostol use have also been reported for women receiving diclofenac sodium/misoprostol (see below). Postmenopausal vaginal bleeding may be related to administration of diclofenac sodium/misoprostol. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology *[see Boxed Warnings, Contraindications (4) and Warnings and Precautions (5)]*.

Other adverse experiences reported occasionally with diclofenac sodium/misoprostol, diclofenac or other NSAIDs, or misoprostol are:

Body as a whole: asthenia, fatigue, malaise.

Central and peripheral nervous system: dizziness, drowsiness, headache, insomnia, paresthesia, vertigo.

Digestive: anorexia, appetite changes, constipation, dry mouth, dysphagia, esophageal ulceration, esophagitis, eructation, gastritis, gastroesophageal reflux, GI neoplasm benign, peptic ulcer, tenesmus, vomiting.

Female reproductive disorders: breast pain, dysmenorrhea, menstrual disorder, menorrhagia, vaginal hemorrhage.

Hemic and lymphatic system: epistaxis, leukopenia, melena, purpura, decreased hematocrit.

Metabolic and nutritional: alanine aminotransferase increased, alkaline phosphatase

increased, aspartate aminotransferase increased, dehydration, hyponatremia.

Musculoskeletal system: arthralgia, myalgia.

Psychiatric: anxiety, concentration impaired, depression, irritability.

Respiratory system: asthma, coughing, hyperventilation.

Skin and appendages: alopecia, eczema, pemphigoid reaction, photosensitivity, sweating increased, pruritus.

Special senses: taste perversion, tinnitus.

Renal and urinary disorders: dysuria, nocturia, polyuria, proteinuria, urinary tract infection.

Vision: diplopia.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval of diclofenac sodium/misoprostol, diclofenac or misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliable estimate their frequency or establish a causal relationship to drug exposure.

Body as a whole: death, fever, infection, sepsis, chills, edema.

Cardiovascular system: arrhythmia, atrial fibrillation, congestive heart failure, hypertension, hypotension, increased creatine phosphokinase (CPK), increased lactate dehydrogenase (LDH), myocardial infarction, palpitations, phlebitis, premature ventricular contractions, syncope, tachycardia, vasculitis.

Central and peripheral nervous system: coma, convulsions, hyperesthesia, hypertonia, hypoesthesia, meningitis, migraine, neuralgia, somnolence, stroke, tremor.

Congenital, familial and genetic disorders: birth defects.

Digestive: enteritis, GI bleeding, glossitis, heartburn, hematemesis, hemorrhoids, intestinal perforation, stomatitis and ulcerative stomatitis.

Female reproductive disorders: intermenstrual bleeding, leukorrhea, vaginitis, uterine cramping, uterine hemorrhage.

Hemic and lymphatic system: agranulocytosis, anemia, aplastic anemia, coagulation time increased, ecchymosis, eosinophilia, hemolytic anemia, leukocytosis, lymphadenopathy, pancytopenia, pulmonary embolism, rectal bleeding, thrombocythemia, thrombocytopenia.

Hypersensitivity: angioedema, laryngeal/pharyngeal edema, urticaria.

Liver and biliary system: abnormal hepatic function, bilirubinemia, liver failure, pancreatitis, hepatitis, jaundice.

Male reproductive disorders: impotence, perineal pain.

Metabolic and nutritional: blood urea nitrogen (BUN) increased, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, periorbital edema, porphyria, weight changes, fluid retention.

Pregnancy, puerperium and perinatal conditions: abnormal uterine contractions, uterine

rupture/perforation, retained placenta, amniotic fluid embolism, incomplete abortion, premature birth, fetal death.

Psychiatric: confusion, disorientation, dream abnormalities, hallucinations, nervousness, paranoia, psychotic reaction.

Reproductive system and breast disorders: female fertility decreased.

Respiratory system: dyspnea, pneumonia, respiratory depression.

Skin and appendages: acne, bruising, erythema multiforme, exfoliative dermatitis, pruritus ani, rash, skin ulceration, Stevens-Johnson syndrome, toxic epidermal necrolysis, cutaneous reactions (bullous eruption).

Special senses: hearing impairment, taste loss.

Renal and urinary disorders: cystitis, hematuria, interstitial nephritis, micturition frequency, nephrotic syndrome, oliguria, papillary necrosis, renal failure, glomerulonephritis membranous, glomerulonephritis minimal lesion, glomerulonephritis.

Vision: amblyopia, blurred vision, conjunctivitis, glaucoma, iritis, lacrimation abnormal, night blindness, vision abnormal.

7 DRUG INTERACTIONS

See Table 1 for clinically significant drug interactions with diclofenac and misoprostol.

Table 1: Clinically Significant Drug Interactions with Diclofenac and Misoprostol

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Diclofenac and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of diclofenac and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of diclofenac sodium/misoprostol with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding *[see Warnings and Precautions (5.12)]*.
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin

Impact:	was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone *[see Warnings and Precautions (5.3)]*.
Intervention:	Concomitant use of diclofenac sodium/misoprostol and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding *[see Warnings and Precautions (5.12)]*. Diclofenac sodium/misoprostol is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• The concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the clinical need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter. • During concomitant use of diclofenac sodium/misoprostol and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of diclofenac sodium/misoprostol and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function *[see Warnings and Precautions (5.7)].*
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of diclofenac sodium/misoprostol with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects *[see Warnings and Precautions (5.7)]*.
Digoxin	

Clinical Impact:	The concomitant use of diclofenac with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of diclofenac sodium/misoprostol and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of diclofenac sodium/misoprostol and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of diclofenac sodium/misoprostol and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of diclofenac and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of diclofenac sodium/misoprostol and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of diclofenac with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy *[see Warnings and Precautions (5.3)].*
Intervention:	The concomitant use of diclofenac sodium/misoprostol with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of diclofenac and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of diclofenac sodium/misoprostol and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. Avoid diclofenac sodium/misoprostol for a period of two days before, the day of, and two days following administration of pemetrexed.
Antacids	
Clinical Impact:	Antacids reduce the bioavailability of misoprostol acid. Antacids may also delay absorption of diclofenac. Magnesium-containing antacids exacerbate misoprostol-associated diarrhea.

Intervention:	Concomitant use of diclofenac sodium/misoprostol and magnesium-containing antacids is not recommended.
Corticosteroids	
Clinical Impact:	Concomitant use of corticosteroids with diclofenac may increase the risk of GI ulceration or bleeding.
Intervention	Monitor patients with concomitant use of diclofenac sodium/misoprostol with corticosteroids for signs of bleeding *[see Warnings and Precautions (5.3)]*.
CYP2C9 Inhibitors or Inducers	
Clinical Impact:	Diclofenac is metabolized by cytochrome P450 enzymes, predominantly by CYP2C9. Co-administration of diclofenac with CYP2C9 inhibitors (e.g., voriconazole) may enhance the exposure and toxicity of diclofenac *[see Clinical Pharmacology (12.3)]* whereas co-administration with CYP2C9 inducers (e.g., rifampin) may lead to compromised efficacy of diclofenac.
Intervention:	CYP2C9 inhibitors: When concomitant use of CYP2C9 inhibitors is necessary, the total daily dose of diclofenac should not exceed the lowest recommended dose of diclofenac sodium/misoprostol 50 twice daily *[*see *Dosage and Administration (2.4)]*. CYP2C9 inducers: A dosage adjustment may be warranted when diclofenac sodium/misoprostol is administered with CYP2C9 inducers. Administer the separate products of misoprostol and diclofenac if a higher dose of diclofenac is deemed necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Diclofenac sodium/misoprostol is contraindicated in pregnant women *[see Contraindications (4)]*. If a woman becomes pregnant while taking diclofenac sodium/misoprostol, discontinue the drug and advise the woman of the potential risks to her and to a fetus.

There are no adequate and well-controlled studies of diclofenac sodium/misoprostol in pregnant women; however, there is information available about the active drug components of diclofenac sodium/misoprostol, diclofenac sodium and misoprostol. Administration of misoprostol to pregnant women can cause uterine rupture, abortion, premature birth, or birth defects *[see Warnings and Precautions (5.1)]*. Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient, but the drug's teratogenic mechanism has not been demonstrated. Use of NSAIDS, including diclofenac a component of diclofenac sodium/misoprostol, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment *(see Data).* There are clinical considerations when misoprostol and diclofenac are used in pregnant women *(see Clinical Considerations)*. In reproduction studies with pregnant rabbits, there were no skeletal or visceral

malformations when the combination of diclofenac sodium and misoprostol was administered during organogenesis at doses less than the maximum recommended human doses (MRHD); however, embryotoxicity was observed at this exposure *(see Data)*. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre- and post-implantation loss.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Maternal Adverse Reactions

Misoprostol may produce uterine contractions, uterine bleeding, and expulsion of the products of conception. Misoprostol has been used to ripen the cervix, to induce labor, and to treat postpartum hemorrhage, outside of its approved indication. A major adverse effect of these uses is hyperstimulation of the uterus. Uterine rupture, amniotic fluid embolism, severe bleeding, shock, and maternal death have been reported when misoprostol was administered to pregnant women to induce labor to induce abortion beyond the eighth week of pregnancy. Higher doses of misoprostol, including the 100 mcg tablet, may increase the risk of complications from uterine hyperstimulation. Diclofenac sodium/misoprostol, which contains 200 mcg of misoprostol, is likely to have a greater risk of uterine hyperstimulation than the 100 mcg tablet of misoprostol. Abortions caused by misoprostol may be incomplete.

Cases of amniotic fluid embolism, which resulted in maternal and fetal death, have been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, and pelvic pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Diclofenac sodium/misoprostol is contraindicated in pregnant women *[see Contraindications (4)]*.

If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

Fetal/Neonatal Adverse Reactions

Misoprostol

Misoprostol may endanger pregnancy (may cause abortion) and thereby cause harm to the fetus when administered to a pregnant woman. Use of misoprostol for the induction of labor in the third trimester was associated with uterine hyperstimulation with resulting changes in the fetal heart rate (fetal bradycardia) and fetal death (misoprostol is not approved for this use). Diclofenac sodium/misoprostol is contraindicated in pregnant women *[see Contraindications (4)]*.

Diclofenac

Premature Closure of Fetal Ductus Arteriosus:

NSAIDs, including diclofenac, can cause premature closure of the fetal ductus arteriosus at about 30 weeks gestation and later in pregnancy *(see Data)*.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including diclofenac, at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment *(see Data)*.

Labor or Delivery

There are no studies on the effects of diclofenac sodium/misoprostol or diclofenac during labor or delivery. In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth. In humans, some case reports and studies have associated misoprostol with risk of stillbirth, uterine hyperstimulation, perineal tear, amniotic fluid embolism, severe bleeding, shock, uterine rupture and death. The risk of uterine rupture associated with misoprostol use in pregnancy may occur at any gestational age, and increases with advancing gestational age and with prior uterine surgery, including cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

Data

Human Data

Misoprostol

Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects.

Diclofenac

Data from observational studies regarding potential embryo-fetal risks of NSAID use (including diclofenac) in the first or second trimesters of pregnancy are inconclusive.

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude

establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

The reproductive and developmental effects of both the combination of diclofenac sodium and misoprostol and each component of diclofenac sodium/misoprostol alone have been studied in animals. In all studies there was no evidence of teratogenicity. In an oral teratology study in pregnant rabbits, diclofenac sodium/misoprostol was administered at dose combinations (diclofenac and misoprostol, 250:1 ratio) up to 10 mg/kg/day diclofenac sodium (120 mg/m^2/day, 0.8 times the MRHD based on body surface area) and 0.04 mg/kg/day misoprostol (0.48 mg/m^2/day, 0.8 times the MRHD based on body surface area) and there was no evidence of teratogenicity. At the high dose, there was evidence of embryotoxicity (resorption and decreased fetal body weight) and maternal toxicity (decreased food intake and weight gain).

In oral teratology studies with misoprostol in pregnant rats at doses up to 1.6 mg/kg/day (9.6 mg/m^2/day, 16 times the MRHD based on body surface area) and pregnant rabbits at doses up to 1.0 mg/kg/day (12 mg/m^2/day, 20 times the MRHD based on body surface area), there was no evidence of teratogenicity.

In oral teratology studies with diclofenac sodium in pregnant mice at doses up to 20 mg/kg/day (60 mg/m^2/day, 0.4 times the MRHD based on body surface area), pregnant rats at doses up to 10 mg/kg/day (60 mg/m^2/day, 0.4 times the MRHD based on body surface area) and pregnant rabbits at doses up to 10 mg/kg/day (120 mg/m^2/day, 0.8 times the MRHD based on body surface area), there was no evidence of teratogenicity.

8.2 Lactation

Risk Summary

No lactation studies have been conducted with diclofenac sodium/misoprostol; however, limited published literature reports that diclofenac and the active metabolite of misoprostol are present in breast milk *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for diclofenac sodium/misoprostol and any potential adverse effects on the breastfed infant from the diclofenac sodium/misoprostol or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Diclofenac sodium/misoprostol is not recommended in women of childbearing potential *[see Warnings and Precautions (5.1)]*. If diclofenac sodium/misoprostol is prescribed, patients must be advised of the abortifacient property and warned not to give the drug to others.

Pregnancy Testing

Verify pregnancy status for females of reproductive potential within 2 weeks prior to initiating diclofenac sodium/misoprostol.

Contraception

Females

Diclofenac sodium/misoprostol can cause fetal harm when administered to a pregnant woman *[see Contraindications (4) and Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with diclofenac sodium/misoprostol.

Diclofenac sodium/misoprostol may be prescribed if the patient:

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin diclofenac sodium/misoprostol only on the second or third day of the next normal menstrual period.

Advise females to inform their healthcare provider of a known or suspected pregnancy.

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including diclofenac, a component of diclofenac sodium/misoprostol, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women *[see Clinical Pharmacology (12.1)].* Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including diclofenac sodium/misoprostol, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Safety and effectiveness of diclofenac sodium/misoprostol in pediatric patients have not been established.

8.5 Geriatric Use

Geriatric patients (those 65 years of age and older), compared to younger adult patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions *[see Warnings and Precautions (5.2, 5.3, 5.7)]*. In addition, the risk of diclofenac-associated adverse reactions may be greater in geriatric patients with renal impairment or those taking concomitant ACE inhibitors or ARBs *[see Drug Interactions (7) and Use in Specific Populations (8.6)]*.

Avoid use of diclofenac sodium/misoprostol in geriatric patients with cardiovascular and/or renal risk factors. If use cannot be avoided, use the lowest recommended dosage for the shortest duration and monitor for cardiac and renal adverse reactions *[see Dosage and Administration (2.1)]*. Monitor renal function in geriatric patients during treatment with diclofenac sodium/misoprostol, especially in patients with concomitant use of ACE inhibitors or ARBs.

Of the 2,184 patients in clinical studies with diclofenac sodium/misoprostol, 557 (25.5%) were 65 years of age and over. No overall differences in effectiveness were observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in effectiveness between geriatric patients and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

No clinically meaningful differences in the pharmacokinetics of diclofenac and misoprostol were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3)].*

8.6 Renal Impairment

Diclofenac and misoprostol are primarily excreted by the kidney. Long-term administration of NSAIDs has resulted in renal toxicity. Correct volume status in dehydrated or hypovolemic patients prior to initiating diclofenac sodium/misoprostol. Monitor renal function, especially during concomitant use of ACE inhibitors or ARBs. Also, monitor renal function in patients with hepatic impairment. Avoid the use of diclofenac sodium/misoprostol in patients with advanced renal disease. If use cannot be avoided in patients with advanced renal disease, use the lowest dosage for the shortest duration, monitor the patient's renal function and monitor for clinical signs of worsening renal function *[see Warnings and Precautions (5.7), Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Manage patients with symptomatic and supportive care following an acute NSAID overdosage. There are no specific antidotes. It is advisable to contact a poison control center (1-800-222-1222) to determine the latest recommendations because strategies for the management of overdose are continually evolving.

The toxic dose of diclofenac sodium/misoprostol has not been determined. However, signs of overdosage from the components of the product have been described.

<u>Diclofenac</u>

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare *[see Warnings and Precautions (5.2, 5.3, 5.5, 5.7)]*.

Clinical signs that may suggest diclofenac sodium overdose include GI complaints, confusion, drowsiness, or general hypotonia.

If gastric decontamination may be potentially beneficial to the patient, e.g., short time since ingestion or a large overdosage (5 to 10 times the recommended dosage), consider emesis and/or activated charcoal (60 grams to 100 grams in adults, 1 gram to 2 grams per kg of body weight in pediatric patients) and/or an osmotic cathartic in symptomatic patients. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

<u>Misoprostol</u>

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of GI discomfort being reported. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia.

Diclofenac sodium/misoprostol

Symptoms of acute overdosage with diclofenac sodium/misoprostol should be treated with supportive and symptomatic therapy. There are no specific antidotes. In case of acute overdosage, emesisis and/or gastric lavage may be considered dependent upon amount ingested and time since ingestion. The use of oral activated charcoal may help to reduce the absorption of diclofenac sodium and misoprostol. Induced diuresis may be beneficial because diclofenac sodium and misoprostol metabolites are excreted in the urine. The effect of dialysis or hemoperfusion on the elimination of diclofenac sodium (99% protein bound) and misoprostol acid remains unproven.

11 DESCRIPTION

Diclofenac sodium/misoprostol is a combination product containing diclofenac sodium, an NSAID with analgesic properties, and misoprostol, a gastrointestinal (GI) mucosal protective prostaglandin-1 (PGE1) analog. Diclofenac sodium/misoprostol tablets are white to off-white, round, biconvex, and approximately 11 mm in diameter. Each tablet consists of an enteric-coated core containing 50 mg (diclofenac sodium/misoprostol 50) or 75 mg (diclofenac sodium/misoprostol 75) of diclofenac sodium (equivalent to 46.39 mg or 69.58 mg of diclofenac, respectively) surrounded by an outer mantle containing 200 mcg misoprostol.

Diclofenac sodium is a phenylacetic acid derivative that is a white to off-white, virtually odorless, crystalline powder. Diclofenac sodium is freely soluble in methanol, soluble in ethanol, and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water. Its chemical formula and name are:

$C_{14}H_{10}Cl_2NO_2Na$ [M.W. = 318.14] 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt.

Misoprostol is a water-soluble, viscous liquid that contains approximately equal amounts of two diastereomers. Its chemical formula and name are:

$C_{22}H_{38}O_5$ [M.W. = 382.54] (±) methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.

Inactive ingredients in diclofenac sodium/misoprostol include: colloidal silicon dioxide; crospovidone; hydrogenated castor oil; hypromellose; lactose; magnesium stearate; methacrylic acid copolymer; microcrystalline cellulose; povidone (polyvidone) K-30; sodium hydroxide; starch (corn); talc; triethyl citrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diclofenac sodium/misoprostol is a combination product containing diclofenac sodium, an NSAID with analgesic, anti-inflammatory and antipyretic properties, and misoprostol, a GI mucosal protective prostaglandin-1 (PGE1) analog.

Diclofenac

The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Diclofenac is a potent inhibitor of prostaglandin (PG) synthesis in vitro. Diclofenac concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Misoprostol

Misoprostol is a synthetic PGE1 analog with gastric antisecretory and mucosal protective properties. NSAIDs inhibit prostaglandin synthesis. A deficiency of prostaglandins within the gastric and duodenal mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by NSAIDs.

Misoprostol can increase bicarbonate and mucus production, but it has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to differentiate whether the ability of misoprostol to reduce the risk of gastric and duodenal ulcers is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using titrated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereo-specific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol, over the range of 50 mcg to 200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter-lived, and only the 200 mcg dose had substantial effects on nocturnal secretion or on histamine- and meal- stimulated secretion.

Misoprostol also produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor intrinsic factor output.

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

The pharmacokinetic profiles of diclofenac and misoprostol administered as the fixed combination (diclofenac sodium/misoprostol 50 or 75) are similar to the profiles when the two drugs are administered as separate tablets (see Table 2). No pharmacokinetic interaction between the two drugs has been observed following multiple dosing. The diclofenac total exposure [area under the curve (AUC)] is dose-proportional within the

range of 25 mg to 150 mg. Approximately dose-proportional increase in misoprostol exposure was also observed within the range of 200 mcg to 400 mcg. Neither diclofenac nor misoprostol accumulated in plasma following repeated doses of diclofenac sodium/misoprostol given every 12 hours under fasted conditions.

Table 2: Pharmacokinetic Parameters of Diclofenac and Misoprostol Acid Following Single Oral Doses of Diclofenac Sodium/Misoprostol or Separate Products in Healthy Subjects

MISOPROSTOL ACID Mean (SD)			
Treatment (n=36)	**C_{max} (pg/mL)**	**T_{max} (hr)**	**$AUC_{(0-4h)}$ (pg·hr/mL)**
Diclofenac sodium/misoprostol 50	441 (137)	0.30 (0.13)	266 (95)
Misoprostol	478 (201)	0.30 (0.10)	295 (143)
Diclofenac sodium/misoprostol 75	304 (110)	0.26 (0.09)	177 (49)
Misoprostol	290 (130)	0.35 (0.12)	176 (58)
DICLOFENAC Mean (SD)			
Treatment (n=36)	**C_{max} (ng/mL)**	**T_{max} (hr)**	**$AUC_{(0-12h)}$ (ng·hr/mL)**
Diclofenac sodium/misoprostol 50	1207 (364)	2.4 (1.0)	1380 (272)
Diclofenac Sodium	1298 (441)	2.4 (1.0)	1357 (290)
Diclofenac sodium/misoprostol 75	2025 (2005)	2.0 (1.4)	2773 (1347)
Diclofenac Sodium	2367 (1318)	1.9 (0.7)	2609 (1185)

SD: Standard deviation of the mean; AUC: Area under the curve; C_{max}: Peak concentration; T_{max}: Time to peak concentration

Absorption

Diclofenac: Diclofenac is completely absorbed from the GI tract after oral administration under fasted condition, and peak plasma levels are achieved in 2 hours (range 1–4 hours), and the area under the plasma concentration curve (AUC) is dose-proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose-proportional and are approximately 1.5 and 2.0 mcg/mL for 50 mg and 75 mg doses, respectively. The diclofenac in diclofenac sodium/misoprostol is in a pharmaceutical formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH environment of the duodenum. Only 50% of the absorbed dose is systemically available due to first pass metabolism (i.e., oral bioavailability is 50%).

Misoprostol: Misoprostol is rapidly absorbed following oral administration of diclofenac sodium/misoprostol, and misoprostol acid (active metabolite) reaches a maximum plasma concentration in approximately 20 minutes. Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food, and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid; this effect does not appear to be clinically important.

Food decreases the multiple-dose bioavailability profile of diclofenac sodium/misoprostol

50 and diclofenac sodium/misoprostol 75.

Distribution

Diclofenac: The volume of distribution of diclofenac is approximately 0.55 L/kg. More than 99% of diclofenac is bound to plasma albumin.

Misoprostol: The plasma protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

After a single oral dose of misoprostol to nursing mothers, misoprostol acid was excreted in breast milk. The maximum concentration of misoprostol acid in expressed breast milk was achieved within 1 hour after dosing and was 7.6 pg/mL (CV 37%) and 20.9 pg/mL (CV 77%) after single 200 mcg and 600 mcg misoprostol administration, respectively. The misoprostol acid concentrations in breast milk declined to <1 pg/mL at 5 hours post-dose. These data may not reflect drug level in mature milk and in a daily dosing regimen for osteoarthritis or rheumatoid arthritis.

Elimination

Metabolism

Diclofenac: Metabolism is predominantly mediated via CYP2C9 in the liver. Five metabolites (4'hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac) have been identified. The major metabolite (4'-hydroxy-diclofenac) has very weak pharmacologic activity.

Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy-diclofenac.

Misoprostol: Undergoes rapid and extensive metabolism to its biologically active metabolite, misoprostol acid.

Excretion

Diclofenac: Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine and 35% in the bile. The elimination half-life of diclofenac is approximately 2 hours. The clearance of diclofenac is approximately 350 mL/min (equivalent to 21 L/h).

Conjugates of unchanged diclofenac account for 5% to 10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20% to 30% of the dose excreted in the urine and for 10% to 20% of the dose excreted in the bile.

Conjugates of three other metabolites together account for 10% to 20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life = 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

Misoprostol: After oral administration of radio-labeled misoprostol, approximately 70% of detected radioactivity appears in the urine. The elimination half-life is approximately 30 minutes.

Specific Populations

Geriatric Patients

No differences in the pharmacokinetics of diclofenac were observed in geriatric subjects (66 to 81 years; N=10) compared to younger adult subjects (26 to 46 years; N=10) following administration of diclofenac 50 mg twice daily for 4 weeks.

Though the mean AUC value of misoprostol acid for elderly subjects was 41% higher in geriatric healthy subjects (mean age, 69.5±4.6 years, N=24) compared to younger adult healthy subjects (mean age, 25.4±4.2 years, N=24) following single dose of misoprostol 400 µg, the increase in exposure is not clinically meaningful.

In a multiple-dose crossover study of diclofenac sodium/misoprostol administered twice daily to 24 subjects aged 65 years of age and older, misoprostol did not affect the pharmacokinetics of diclofenac *[see Use in Specific Populations (8.5)]*.

Racial or Ethnic Groups

Pharmacokinetic differences due to race have not been identified.

Patients with Renal Impairment

In patients with renal impairment (N=5, creatinine clearance 3 to 42 mL/min) following intravenous administration of 50 mg diclofenac, AUC values and elimination rates were comparable to those in healthy subjects.

Pharmacokinetic studies with misoprostol in patients with severe renal impairment requiring hemodialysis (n=8, mean creatinine clearance 6.2±3.3 mL/min/1.73m^2) who received a single dose of 400 mcg misoprostol during a interdialytic period showed an approximate doubling of elimination half-life, C_{max}, and AUC of misoprostol acid compared to healthy subjects *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubin, N=10), diclofenac concentrations and urinary elimination values following administration of 100 mg oral solution were comparable to those in healthy subjects.

In a study of subjects with mild to moderate hepatic impairment, mean misoprostol acid AUC and C_{max} showed approximately twice high as the mean values obtained in healthy subjects. Three subjects who had the lowest antipyrine and lowest indocyanine green clearance values had the highest misoprostol acid AUC and C_{max} values.

Drug Interaction Studies

Diclofenac

Aspirin: When diclofenac sodium/misoprostol was administered with aspirin, the protein binding of diclofenac was reduced, although the clearance of the free diclofenac was not altered. The clinical significance of this interaction is not known. See Table 1 for clinically

significant drug interactions of NSAIDs with aspirin *[see Drug Interactions (7)]*.

Voriconazole: When a single dose diclofenac (50 mg) was coadministered with the last dose of voriconazole (400 mg every 12 hours on Day 1, followed by 200 mg every 12 hours on Day 2), the mean C_{max} and AUC of diclofenac were increased by 114% and 78%, respectively, when compared to diclofenac alone *[see Drug Interactions (7)]*.

In vitro, diclofenac interferes minimally with the protein binding of prednisolone (10% decrease in binding). Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence, in vitro, on the protein binding of diclofenac in human serum.

Other drugs: In small groups of patients (7 to 10 patients/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline or digitoxin did not significantly affect C_{max} and AUC of diclofenac.

Misoprostol

Diazepam: Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

Other drugs: Pharmacokinetic studies also showed a lack of drug interaction with antipyrine or propranolol given with misoprostol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies to evaluate the potential for carcinogenesis and animal studies to evaluate the effects on fertility have been performed with each component of diclofenac sodium/misoprostol given alone.

In a 24 month rat carcinogenicity study, misoprostol administered orally at doses up to 2.4 mg/kg/day (14.4 mg/m^2/day, 24 times the MRHD of 0.6 mg/m^2/day) was not tumorigenic. In a 21 month mouse carcinogenicity study, misoprostol administered orally at doses up to 16 mg/kg/day (48 mg/m^2/day), 80 times the MRHD based on body surface area, was not tumorigenic.

In a 24 month rat carcinogenicity study, diclofenac sodium administered orally at up to 2 mg/kg/day (12 mg/m^2/day) was not tumorigenic. In a 24 month mouse carcinogenicity study, oral diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m^2/day, 0.006 times the MRHD based on body surface area) in males and 1 mg/kg/day (3 mg/m^2/day, 0.02 times the MRHD based on body surface area) in females was not tumorigenic.

Mutagenesis

Diclofenac sodium and misoprostol combination in 250:1 ratio was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the rat lymphocyte chromosome aberration test, or the mouse bone marrow micronucleus test.

Impairment of Fertility

The effects of diclofenac sodium and misoprostol on male or female fertility have not been studied in animals; however, there are data with diclofenac sodium and misoprostol given alone. Misoprostol, when administered to male and female breeding rats in an oral dose range of 0.1 to 10 mg/kg/day (0.6 to 60 mg/m^2/day, 1 to 100 times the MRHD based on body surface area) produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose (60 mg/m^2/day, 100 times the MRHD based on body surface area). Diclofenac sodium at oral doses up to 4 mg/kg/day (24 mg/m^2/day, 0.16 times the MRHD based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology

A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse during long-term toxicology studies with misoprostol. No such increase has been observed in humans administered misoprostol for up to 1 year. An apparent response of the female mouse to misoprostol in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with misoprostol.

14 CLINICAL STUDIES

Osteoarthritis

Diclofenac sodium, as a single ingredient or in combination with misoprostol, has been shown to be effective in the management of the signs and symptoms of osteoarthritis.

Rheumatoid Arthritis

Diclofenac sodium, as a single ingredient or in combination with misoprostol, has been shown to be effective in the management of the signs and symptoms of rheumatoid arthritis.

Upper Gastrointestinal Safety

Diclofenac, and other NSAIDs, have caused serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine. Misoprostol has been shown to reduce the incidence of endoscopically diagnosed NSAID-induced gastric and duodenal ulcers. In a 12-week, randomized, double-blind, dose-response study, misoprostol 200 mcg administered four, three or two times a day, was significantly more effective than placebo in reducing the incidence of gastric ulcer in osteoarthritis and rheumatoid arthritis patients using a variety of NSAIDs. The three times a day regimen was therapeutically equivalent to misoprostol 200 mcg four times a day with respect to the prevention of gastric ulcers. Misoprostol 200 mcg given two times a day was less effective than 200 mcg given three or four times a day. The incidence of NSAID-induced duodenal ulcer was also significantly reduced with all three regimens of misoprostol compared to placebo (see Table 3).

Table 3

Misoprostol 200 mcg Dosage Regimen				

	Placebo	two times a day	three times a day	four times a day
Gastric ulcer	11%	6%*	3%*	3%*
Duodenal ulcer	6%	2%*	3%*	1%*

* Misoprostol significantly different from placebo (p<0.05)

N=1623; 12 weeks

Results of a study in 572 patients with osteoarthritis demonstrate that patients receiving diclofenac sodium/misoprostol have a lower incidence of endoscopically defined gastric ulcers compared to patients receiving diclofenac sodium (see Table 4).

Table 4

Osteoarthritis patients with history of ulcer or erosive disease (N=572), 6 weeks	**Incidence of ulcers**	
	Gastric	**Duodenal**
Diclofenac sodium/misoprostol 50 three times a day	3%*	6%
Diclofenac sodium/misoprostol 75 two times a day	4%*	3%
Diclofenac sodium 75 mg two times a day	11%	7%
Placebo	3%	1%

* Statistically significantly different from diclofenac (p<0.05)

16 HOW SUPPLIED/STORAGE AND HANDLING

Diclofenac sodium and misoprostol delayed-release tablets are supplied as:

- 50 mg diclofenac sodium and 200 mcg misoprostol as round, biconvex, white to off-white tablets imprinted with a "50" in the middle on one side and "G" and "0028" on the other.
- 75 mg diclofenac sodium and 200 mcg misoprostol as round, biconvex, white to off-white tablets imprinted with a "75" in the middle on one side and "G" and "0029" on the other.

The dosage strengths are supplied in:

Strength		**NDC Number**	**Size**
Diclofenac sodium/misoprostol 50	50 mg diclofenac sodium and 200 mcg misoprostol	59762-0028-1	bottle of 60
		59762-0028-2	bottle of 90
Diclofenac	75 mg diclofenac sodium	59762-0029-1	bottle of 60

sodium/misoprostol 75	and 200 mcg misoprostol	59762-0029-1	bottle of 60

Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Inform patients, families, or their caregivers of the following information before initiating therapy with diclofenac sodium/misoprostol and periodically during the course of ongoing therapy.

Uterine Rupture, Abortion, Premature Birth, or Birth Defects with Misoprostol and Embryo-Fetal Toxicity with NSAIDs

- Advise females that diclofenac sodium/misoprostol is contraindicated in pregnant women. Use of misoprostol, a component of diclofenac sodium/misoprostol during pregnancy can result in maternal and fetal harm, including uterine rupture, abortion, premature birth, or birth defects. Use of diclofenac may cause oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus.
- Advise patients not to give diclofenac sodium/misoprostol to others.
- Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with diclofenac sodium/misoprostol. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)]*.

Infertility

Advise females of reproductive potential that diclofenac sodium/misoprostol may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women *[see Use in Specific Populations (8.3)]*.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately *[see Warnings and Precautions (5.2)]*.

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea,

fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop diclofenac sodium/misoprostol and seek immediate medical therapy *[see Warnings and Precautions (5.4)]*.

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur *[see Warnings and Precautions (5.6)]*.

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur *[see Contraindications (4) and Warnings and Precautions (5.8)]*.

Serious Skin Reactions, including DRESS

Advise patients to stop taking diclofenac sodium/misoprostol immediately if they develop any type of rash or fever and contact their healthcare provider as soon as possible *[see Warnings and Precautions (5.10), (5.11)].*

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of diclofenac sodium/misoprostol with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy *[see Warnings and Precautions (5.3) and Drug Interactions (7)].* Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with diclofenac sodium/misoprostol until they talk to their healthcare provider *[see Drug Interactions (7)]*.

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LAB-0552-11.0

MEDICATION GUIDE
Medication Guide for
DICLOFENAC SODIUM/MISOPROSTOL
(diclofenac sodium and misoprostol delayed-release tablets)

for oral use

What is the most important information I should know about diclofenac sodium/misoprostol?

Diclofenac sodium/misoprostol contains diclofenac (a nonsteroidal anti-inflammatory drug (NSAID)) and misoprostol, and can cause uterus to tear (uterine rupture), abortion, premature birth, or birth defects. The risk of uterine rupture increases as your pregnancy advances, if you have given birth to 5 or more children, and if you have had surgery on the uterus, such as a cesarean delivery.

Do not take diclofenac sodium/misoprostol if you are pregnant.

- Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with diclofenac sodium/misoprostol. If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with diclofenac sodium/misoprostol. Females who are able to become pregnant should use an effective form of birth control (contraception) during treatment with diclofenac sodium/misoprostol.

What is the most important information I should know about medicines containing Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take NSAID containing medicines right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

Avoid taking NSAID containing medicines after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "antiplatelet drugs", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- older age
- poor health

- smoking
- drinking alcohol
- advanced liver disease
- bleeding problems

NSAID containing medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What is diclofenac sodium/misoprostol?
Diclofenac sodium/misoprostol contains 2 medicines:

1. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). **See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?**
2. Misoprostol is a medicine used to protect the lining of the esophagus, stomach and intestines while taking diclofenac.

Diclofenac sodium/misoprostol is a prescription medicine used to treat:

- symptoms of osteoarthritis or rheumatoid arthritis in adults at high risk of developing stomach (gastric) and intestinal (duodenal) ulcers while taking NSAIDs.

It is not known if diclofenac sodium/misoprostol is safe and effective for use in children.
What are NSAIDs?
NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis.

Who should not take diclofenac sodium/misoprostol?
Do not take diclofenac sodium/misoprostol:

- if you are pregnant.
- right before or after heart bypass surgery.
- if you currently have bleeding in your stomach (gastrointestinal bleeding).
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- if you are allergic to diclofenac sodium and misoprostol, other prostaglandins or any other ingredients in diclofenac sodium/misoprostol. See the end of this Medication Guide for a list of ingredients in diclofenac sodium/misoprostol.

Before taking diclofenac sodium/misoprostol, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems.
- have high blood pressure.
- have heart problems, including a history of heart failure or heart attack.
- have asthma.
- are pregnant or plan to become pregnant. See "Who should not take diclofenac sodium/misoprostol?"
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including

prescription and over-the-counter medicines, vitamins and herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?
NSAIDs can cause serious side effects, including:
See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- asthma attacks in people who have asthma
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.
These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause

ulcers in the stomach and intestines.

- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.
If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Active ingredients: diclofenac sodium, misoprostol.
Inactive ingredients: colloidal silicon dioxide, crospovidone, hydrogenated castor oil, hypromellose, lactose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, povidone (polyvidone) K-30, sodium hydroxide, starch (corn), talc, triethyl citrate.
For more information, go to www.greenstonellc.com or call 1-800-438-1985

GREENSTONE® BRAND

Distributed by:

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Morgantown, WV 26505 U.S.A.

LAB-0801-6.0

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: August 2022

PRINCIPAL DISPLAY PANEL - 50 mg/200 mcg Tablet Bottle Label

ALWAYS DISPENSE WITH MEDICATION GUIDE
NDC 59762-0028-1
60 Tablets

GREENSTONE® BRAND

diclofenac sodium
and misoprostol
delayed-release tablets

50 mg/200 mcg

Rx only

PRINCIPAL DISPLAY PANEL - 75 mg/200 mcg Tablet Bottle Label

ALWAYS DISPENSE WITH MEDICATION GUIDE
NDC 59762-0029-1
60 Tablets

GREENSTONE® BRAND

diclofenac sodium
and misoprostol
delayed-release tablets

75 mg/200 mcg

Rx only

DICLOFENAC SODIUM AND MISOPROSTOL

diclofenac sodium and misoprostol tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59762-0028
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DICLOFENAC SODIUM (UNII: QTG126297Q) (DICLOFENAC - UNII:144O8QL0L1)	DICLOFENAC SODIUM	50 mg
MISOPROSTOL (UNII: 0E43V0BB57) (MISOPROSTOL - UNII:0E43V0BB57)	MISOPROSTOL	200 ug

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (120 .MU.M) (UNII: 68401960MK)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE K30 (UNII: U725QWY32X)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND (biconvex)	**Size**	11mm
Flavor		**Imprint Code**	50;G;0028
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59762-0028-1	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/01/2012	
2	NDC:59762-0028-2	90 in 1 BOTTLE; Type 0: Not a Combination Product	11/01/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

NDA AUTHORIZED GENERIC	NDA020607	11/01/2012	

DICLOFENAC SODIUM AND MISOPROSTOL

diclofenac sodium and misoprostol tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59762-0029
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DICLOFENAC SODIUM (UNII: QTG126297Q) (DICLOFENAC - UNII:144O8QL0L1)	DICLOFENAC SODIUM	75 mg
MISOPROSTOL (UNII: 0E43V0BB57) (MISOPROSTOL - UNII:0E43V0BB57)	MISOPROSTOL	200 ug

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (120 .MU.M) (UNII: 68401960MK)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE K30 (UNII: U725QWY32X)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND (biconvex)	**Size**	11mm
Flavor		**Imprint Code**	75;G;0029
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59762-0029-1	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/01/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA020607	11/01/2012	

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Revised: 6/2024 Greenstone LLC