DICLOFENAC SODIUM AND MISOPROSTOL DELAYED-RELEASE TABLETS

Rx only

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DICLOFENAC SODIUM AND MISOPROSTOL DELAYED-RELEASE TABLETS

CONTRAINDICATIONS AND WARNINGS

DICLOFENAC SODIUM AND MISOPROSTOL DELAYED-RELEASE TABLETS CONTAIN DICLOFENAC SODIUM AND MISOPROSTOL. ADMINISTRATION OF MISOPROSTOL TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN MISOPROSTOL WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY (see also **PRECAUTIONS**). DICLOFENAC SODIUM AND MISOPROSTOL DELAYED-RELEASE TABLETS SHOULD NOT BE TAKEN BY PREGNANT WOMEN (see **CONTRAINDICATIONS**, **WARNINGS** and **PRECAUTIONS**).

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS. DICLOFENAC SODIUM AND MISOPROSTOL DELAYED-RELEASE TABLETS should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of developing gastric or duodenal ulceration or for developing complications from gastric or duodenal ulcers associated with the use of the NSAID (see **WARNINGS**). In such patients, diclofenac sodium and misoprostol delayed-release tablets 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 and misoprostol delayed-release tablets only on the second or third day of the next normal menstrual period.

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS**).
- Diclofenac sodium and misoprostol delayed-release tablets are contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal 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 are at greater risk for serious gastrointestinal events (see **WARNINGS**).

DESCRIPTION Diclofenac sodium and misoprostol delayed-release tablets are a combination product containing diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, and misoprostol, a gastrointestinal (GI) mucosal protective prostaglandin E_1 analog. Diclofenac sodium and misoprostol delayed-release tablets are white circular, biconvex tablets containing 200 mcg misoprostol with off white circular enteric coated inlay tablet containing either 50 or 75 mg of diclofenac sodium and approximately 11.5 mm in diameter.

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 and misoprostol delayed-release tablets include: hydrogenated castor oil; hypromellose; lactose; magnesium stearate; methacrylic acid copolymer; microcrystalline cellulose; povidone (polyvidone) K-30; sodium starch glycolate; starch (corn); talc; triethyl citrate.

CLINICAL PHARMACOLOGY

Pharmacodynamics and pharmacokinetics of diclofenac sodium

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac sodium has shown anti-inflammatory, analgesic and antipyretic properties. The mechanism of action of diclofenac sodium, like other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Diclofenac sodium is completely absorbed from the GI tract after fasting, oral administration. The diclofenac sodium in diclofenac sodium and misoprostol delayed-release tablets 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. Peak plasma levels are achieved in 2 hours (range 1 to 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.

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CYP2C9. 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.

Plasma concentrations of diclofenac sodium decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac sodium is reversibly bound to human plasma albumin.

Diclofenac sodium 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.

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.

Pharmacodynamics and pharmacokinetics of misoprostol

Misoprostol is a synthetic prostaglandin E_1 analog with gastric antisecretory and (in animals) 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 in humans this has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to tell 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 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.

Effects on gastric acid secretion: Misoprostol, over the range of 50 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.

Orally administered misoprostol is rapidly and extensively absorbed, and it undergoes rapid metabolism to its biologically active metabolite, misoprostol acid. Misoprostol acid in diclofenac sodium and misoprostol delayed-release tablets reaches a maximum plasma concentration in about 20 minutes and is, thereafter, quickly eliminated with an elimination $t_{1/2}$ of about 30 minutes. There is high variability in plasma levels of misoprostol acid between and within studies, but mean values after single doses show a linear relationship with dose of misoprostol over the range of 200 to 400 mcg. No accumulation of misoprostol acid was found in multiple-dose studies, and plasma steady state was achieved within 2 days. The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

After oral administration of radio-labeled misoprostol, about 70% of detected radioactivity appears in the urine. 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.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine or propranolol given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

Pharmacokinetics of diclofenac sodium and misoprostol delayed-release tablets

The pharmacokinetics following oral administration of a single dose (see Table 1) or multiple doses of diclofenac sodium and misoprostol delayed-release tablets (diclofenac sodium/misoprostol) to healthy subjects under fasted conditions are similar to the pharmacokinetics of the two individual components.

Table 1

MISOPROSTOL ACID Mean (SD)			
Treatment (n=36)	**C_{max} (pg/mL)**	**t_{max} (hr)**	**$AUC_{(0-4h)}$ (pg·hr/mL)**
Diclofenac sodium and misoprostol delayed-release tablets, 50/0.2 mg	441 (137)	0.30 (0.13)	266 (95)
Cytotec®	478 (201)	0.30 (0.10)	295 (143)
Diclofenac sodium and misoprostol delayed-release tablets, 75/0.2 mg	304 (110)	0.26 (0.09)	177 (49)
Cytotec®	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 and misoprostol delayed-release tablets, 50/0.2 mg	1207 (364)	2.4 (1.0)	1380 (272)
Voltaren®	1298 (441)	2.4 (1.0)	1357 (290)
Diclofenac sodium and misoprostol delayed-release tablets, 75/0.2 mg	2025 (2005)	2.0 (1.4)	2773 (1347)
Voltaren®	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

The rate and extent of absorption of both diclofenac sodium and misoprostol acid from diclofenac sodium and misoprostol delayed-release tablets, 50/0.2 mg and diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg are similar to those from diclofenac sodium and misoprostol formulations each administered alone.

Neither diclofenac sodium nor misoprostol acid accumulated in plasma following repeated doses of diclofenac sodium and misoprostol delayed-release tablets given every 12 hours under fasted conditions. Food decreases the multiple-dose bioavailability profile of diclofenac sodium and misoprostol delayed-release tablets, 50/0.2 mg and diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg.

Specific populations

A 4-week study, comparing plasma level profiles of diclofenac (50 mg bid) in younger (26 to 46 years) versus older (66 to 81 years) adults, did not show differences between age groups (10 patients per age group). In a multiple-dose (bid) crossover study of 24 people aged 65 years or older, the misoprostol contained in diclofenac sodium and misoprostol delayed-release tablets did not affect the pharmacokinetics of diclofenac sodium.

Differences in the pharmacokinetics of diclofenac have not been detected in studies of patients with renal (50 mg intravenously) or hepatic impairment (100 mg oral solution). In patients with renal impairment (N=5, creatinine clearance 3 to 42 mL/min), AUC values and elimination rates were comparable to those in healthy people. In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N=10), diclofenac concentrations and urinary elimination values were comparable to those in healthy people.

Pharmacokinetic studies with misoprostol in patients with varying degrees of renal impairment showed an approximate doubling of $t_{1/2}$, C_{max} and AUC compared to healthy people. In people over 64 years of age, the AUC for misoprostol acid is increased.

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

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 µg and 600 µg misoprostol administration, respectively. The misoprostol acid concentrations in breast milk declined to < 1 pg/mL at 5 hours post-dose.

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 qid, tid or bid, was significantly more effective than placebo in reducing the incidence of gastric ulcer in OA and RA patients using a variety of NSAIDs. The tid regimen was therapeutically equivalent to misoprostol 200 mcg qid with respect to the prevention of gastric ulcers. Misoprostol 200 mcg given bid was less effective than 200 mcg given tid or qid. The incidence of NSAID-induced duodenal ulcer was also significantly reduced with all three regimens of misoprostol compared to placebo (see Table 2).

Table 2				
Misoprostol 200 mcg Dosage Regimen				
	Placebo	**Bid**	**tid**	**qid**
Gastric ulcer	11%	6%*	3%*	3%*
Duodenal ulcer	6%	2%*	3%*	1%*

N=1623; 12 weeks
*Misoprostol significantly different from placebo (p<0.05)

Results of a study in 572 patients with osteoarthritis demonstrate that patients receiving diclofenac sodium and misoprostol delayed-release tablets have a lower incidence of endoscopically defined gastric ulcers compared to patients receiving diclofenac sodium (see Table 3).

Table 3

Osteoarthritis patients with history of ulcer or erosive disease (N=572), 6 weeks	**Incidence of ulcers**	
	Gastric	**Duodenal**
Diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg tid	3%*	6%
Diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg bid	4%*	3%
diclofenac sodium 75 mg bid	11%	7%
placebo	3%	1%

*Statistically significantly different from diclofenac (p<0.05)

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of diclofenac sodium and misoprostol delayed-release tablets and other treatment options before deciding to use diclofenac sodium and misoprostol delayed-release tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

Diclofenac sodium and misoprostol delayed-release tablets are indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. See **WARNINGS, Gastrointestinal Effects - Risk of Ulceration, Bleeding and Perforation** for a list of factors that may increase the risk of NSAID-induced gastric and duodenal ulcers and their complications.

CONTRAINDICATIONS

See boxed **CONTRAINDICATIONS AND WARNINGS** related to misoprostol.

Diclofenac sodium and misoprostol delayed-release tablets should not be taken by pregnant women.

Diclofenac sodium and misoprostol delayed-release tablets are contraindicated in patients with hypersensitivity to diclofenac or to misoprostol or other prostaglandins. Diclofenac sodium and misoprostol delayed-release tablets should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac sodium have been reported in such patients (see **WARNINGS**- **Anaphylactic Reactions**, and **PRECAUTIONS**-**Preexisting Asthma**).

Diclofenac sodium and misoprostol delayed-release tablets are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see boxed **CONTRAINDICATIONS AND WARNINGS**).

WARNINGS

Regarding misoprostol:
See boxed **CONTRAINDICATIONS AND WARNINGS.**

Regarding diclofenac:
See boxed **CONTRAINDICATIONS AND WARNINGS.**

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or 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 does increase the risk of serious GI events (see **WARNINGS, Gastrointestinal Effects - Risk of Ulceration, Bleeding and Perforation**).

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 (see **CONTRAINDICATIONS**).

Hypertension

NSAIDs, including diclofenac sodium and misoprostol delayed-release tablets, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including diclofenac sodium and misoprostol delayed-release tablets, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Diclofenac sodium and misoprostol delayed-release tablets should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects - Risk of Ulceration, Bleeding and Perforation

NSAIDs, including diclofenac sodium and misoprostol delayed-release tablets, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the 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 occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients treated with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

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 a nonsteroidal anti-inflammatory drug 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, heart failure, liver dysfunction, those taking diuretics and ACE-inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

Diclofenac sodium and misoprostol delayed-release tablets contain diclofenac. Diclofenac metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. Therefore, treatment with diclofenac sodium and misoprostol delayed-release tablets is not recommended in these patients with advanced renal disease. If diclofenac sodium and misoprostol delayed-release tablets therapy must be initiated, close monitoring of the patient's renal function is advisable.

Hepatic Effects

In clinical trials with diclofenac sodium and misoprostol delayed-release tablets, meaningful elevation of ALT (SGPT, more than 3 times the ULN [ULN= the upper limit of the normal range]) occurred in 1.6% of 2,184 patients treated with diclofenac sodium and misoprostol delayed-release tablets 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 and misoprostol delayed-release tablets. The misoprostol component of diclofenac sodium and misoprostol delayed-release tablets does not appear to exacerbate the hepatic effects caused by the diclofenac sodium component.

Elevations of one or more liver tests may occur during therapy with diclofenac, a component of diclofenac sodium and misoprostol delayed-release tablets. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e., less than 3 times the ULN), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated 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., more 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 (>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. In another clinical trial where over 17,000 patients received diclofenac for a mean of 18 months, hepatitis was rarely observed.

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 usually occur within 1 to 6 months, 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.

Physicians should measure transaminases 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 and misoprostol delayed-release tablets should be discontinued immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

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

Anaphylactic Reactions

As with other NSAIDs, anaphylactic reactions may occur in patients without known prior exposure to diclofenac sodium and misoprostol delayed-release tablets. Diclofenac sodium and misoprostol delayed-release tablets should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS—Preexisting Asthma**). Anaphylactic reactions may also occur to the misoprostol component of diclofenac sodium and misoprostol delayed-release tablets. Emergency help should be sought in cases where an anaphylactic reaction occurs. Allergic reactions have been reported by less than 0.1% of patients who received diclofenac sodium and misoprostol delayed-release tablets in clinical trials, and there have been rare reports of anaphylaxis in the marketed use of diclofenac sodium and misoprostol delayed-release tablets outside of the United States.

Skin Reactions

NSAIDs, including diclofenac sodium and misoprostol delayed-release tablets, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, diclofenac sodium and misoprostol delayed-release tablets should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

Diclofenac sodium and misoprostol delayed-release tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. The pharmacological activity of diclofenac sodium and misoprostol delayed-release tablets in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

See **WARNINGS.**

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including diclofenac sodium and misoprostol delayed-release tablets. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including diclofenac sodium and misoprostol delayed-release tablets, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving diclofenac sodium and misoprostol delayed-release tablets who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, diclofenac sodium and misoprostol delayed-release tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Aseptic Meningitis

As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. Although it is probably more likely to occur in patients with systemic lupus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on diclofenac, the possibility of it being related to diclofenac should be considered.

Porphyria

The use of diclofenac sodium and misoprostol delayed-release tablets in patients with hepatic porphyria should be avoided. To date, one patient has been described in whom diclofenac sodium probably triggered a clinical attack of porphyria. The postulated mechanism, demonstrated in rats, for causing such attacks by diclofenac sodium, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

Information for patients: Women of childbearing potential using diclofenac sodium and misoprostol delayed-release tablets to treat arthritis should be told that they must not be pregnant when therapy with diclofenac sodium and misoprostol delayed-release tablets is initiated, and that they must use an effective contraception method while taking diclofenac sodium and misoprostol delayed-release tablets. See boxed **CONTRAINDICATIONS AND WARNINGS**.

THE PATIENT SHOULD NOT GIVE DICLOFENAC SODIUM AND MISOPROSTOL DELAYED-RELEASE TABLETS TO ANYONE ELSE. Diclofenac sodium and misoprostol delayed-release tablets have been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she were to become pregnant.

SPECIAL NOTE FOR WOMEN: DICLOFENAC SODIUM AND MISOPROSTOL DELAYED-RELEASE TABLETS contain diclofenac sodium and misoprostol. Misoprostol may cause abortion (sometimes incomplete), premature labor, or birth defects if given to pregnant women.

PATIENT INFORMATION LEAFLET

Read this leaflet before taking diclofenac sodium and misoprostol delayed-release tablets (diclofenac sodium 50 or 75 mg/ misoprostol 200 mcg) and each time your prescription is renewed, because the leaflet may be changed.

Diclofenac sodium and misoprostol delayed-release tablets are being prescribed by your doctor for treatment of your arthritis symptoms while at the same time providing protection from the development of stomach and intestinal ulcers due to the arthritis medication. Diclofenac sodium and misoprostol delayed-release tablets contain diclofenac, an arthritis medication. Diclofenac sodium and misoprostol delayed-release tablets also contain misoprostol to decrease the chance of getting stomach and intestinal ulcers that sometimes develop with NSAID medications. Serious side effects are still possible, however, and you should report to your doctor any signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain or swelling. If signs of liver toxicity occur (nausea, fatigue, lethargy, itching, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), you should stop therapy and seek immediate medical attention.

If signs of an anaphylactic reaction occur (e.g., difficulty breathing, swelling of the face or throat), you should stop therapy and seek immediate medical attention (see **WARNINGS**).

Do not take diclofenac sodium and misoprostol delayed-release tablets if you are pregnant (see boxed **CONTRAINDICATIONS AND WARNINGS**). Diclofenac sodium and misoprostol delayed-release tablets contain diclofenac sodium and misoprostol. Misoprostol can cause abortion (sometimes incomplete which could lead to dangerous bleeding and require hospitalization and surgery), premature birth, or birth defects. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Misoprostol has been reported to cause the uterus to rupture (tear) when given after the eighth week of pregnancy. Rupture (tearing) of the uterus can result in severe bleeding, hysterectomy, and/or maternal or fetal death.

If you become pregnant during therapy with diclofenac sodium and misoprostol delayed-release tablets, stop taking diclofenac sodium and misoprostol delayed-release tablets and contact your doctor immediately. Remember that even if you are using a means of birth control, it is still possible to become pregnant. Should this occur, stop taking diclofenac sodium and misoprostol delayed-release tablets and consult your doctor immediately.

Diclofenac sodium and misoprostol delayed-release tablets are not recommended for nursing mothers.

Diclofenac sodium and misoprostol delayed-release tablets, like other NSAIDs, may cause an increased risk of heart attack, or stroke, which can lead to death. This risk may increase with duration of use. If you have heart disease or risk factors for heart disease, you may be at greater risk (see boxed **CONTRAINDICATIONS AND WARNINGS**). Diclofenac sodium and misoprostol delayed-release tablets should never be used for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see boxed **CONTRAINDICATIONS AND WARNINGS**). Although serious CV events can occur without warning symptoms, ask for medical advice when observing signs and symptoms of chest pain, shortness of breath, weakness, or slurring of speech (see boxed **CONTRAINDICATIONS AND WARNINGS**).

Diclofenac sodium and misoprostol delayed-release tablets, like other NSAIDs, may cause GI discomfort and, rarely, serious GI effects such as ulcers and bleeding, which may result in hospitalization and even death.

Diclofenac sodium and misoprostol delayed-release tablets may cause diarrhea, abdominal pain, upset stomach and/or nausea in some people. In most cases these problems develop during the first few weeks of therapy and stop after about a week with continued treatment. You can minimize possible diarrhea by making sure you take diclofenac sodium and misoprostol delayed-release tablets with meals and by avoiding the use of antacids containing magnesium (if needed, use one containing aluminum or calcium instead). Diclofenac sodium and misoprostol delayed-release tablets should be swallowed whole, and not chewed, crushed or dissolved.

Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take diclofenac sodium and misoprostol delayed-release tablets. If you have prolonged difficulty (more than 7 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.

Diclofenac sodium and misoprostol delayed-release tablets may also cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can lead to death. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see boxed **CONTRAINDICATIONS AND WARNINGS**). This risk may increase with duration of use.

Although serious GI tract ulcerations and bleeding can occur without warning symptoms, ask for medical advice when observing signs and symptoms of ulceration and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis.

(See boxed **CONTRAINDICATIONS AND WARNINGS**.)

Diclofenac sodium and misoprostol delayed-release tablets, like other NSAIDs, may cause serious skin side effects, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis, which may result in hospitalization and even death.

Although serious skin reactions may occur without warning, ask for medical advice when observing signs or symptoms, such as skin rash and blisters, fever, or other signs of hypersensitivity such as itching. Stop the drug immediately at the first appearance of skin rash or any other signs of hypersensitivity and contact your physician as soon as possible.

Take diclofenac sodium and misoprostol delayed-release tablets only according to the directions given by your doctor. Changes in dose should be made only with your doctor's approval.

Do not give diclofenac sodium and misoprostol delayed-release tablets to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and could be dangerous for another person, especially a woman who may be, or could become, pregnant.

This information sheet does not cover all possible side effects of diclofenac sodium and misoprostol delayed-release tablets. See your doctor if you have questions.

Keep out of reach of children.

Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.

This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol

- older age
- having poor health

NSAID medicines should only be used:

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

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)? Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

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

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

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

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

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine 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 of these NSAID medicines 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.

NSAID medicines that need a prescription

Generic Name	**Tradename**
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec(combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Kehh hrofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC- Naprosyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

- Diclofenac sodium and misoprostol delayed-release tablets, like other NSAIDs, may cause serious side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, CARDIOVASCULAR EFFECTS**).
- Diclofenac sodium and misoprostol delayed-release tablets, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulceration and bleeding, and should ask for medical advice when observing any indicative sign or symptoms, including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects - Risk of Ulceration, Bleeding and Perforation**).
- Diclofenac sodium and misoprostol delayed-release tablets, like other NSAIDs, can cause serious skin side effects, such as exfoliative dermatitis, SJS and TEN, which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
- Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
- Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical attention.
- Patients should be informed of the signs of an anaphylactic reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS - Anaphylactic Reactions**).
- In late pregnancy, as with other NSAIDs, diclofenac sodium and misoprostol delayed-release tablets should not be taken because it may cause premature closure of the ductus arteriosus.
- Diclofenac sodium and misoprostol delayed-release tablets should not be taken by nursing mothers.
- Concomitant use of voriconazole increases the systemic exposure to diclofenac. When concomitant voriconazole use is necessary, the total daily dose of diclofenac should not exceed the lowest recommended dose of diclofenac sodium and misoprostol delayed-release tablets 50 mg/0.2 mg twice daily (see **Drug Interactions** and **Dosage and Administration**).

See *PATIENT INFORMATION* at the end of this labeling for important information to discuss with the patient.

Diclofenac sodium and misoprostol delayed-release tablets are available only as a unit-of-use package that includes a leaflet containing patient information. The patient should read the leaflet before taking diclofenac sodium and misoprostol delayed-release tablets and each time the prescription is renewed because the leaflet may have been revised. Keep diclofenac sodium and misoprostol delayed-release tablets out of the reach of children.

Laboratory tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.), or if abnormal liver tests persist or worsen, diclofenac sodium and misoprostol delayed-release tablets should be discontinued.

Effect on blood coagulation: Diclofenac sodium impairs platelet aggregation but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Diclofenac sodium is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed. Misoprostol has not been shown to exacerbate the effects of diclofenac on platelet activity.

Drug Interactions

ACE-inhibitors:

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, may result in deterioration of renal function, including possible acute renal failure. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Aspirin:

When diclofenac sodium and misoprostol delayed-release tablets are administered with aspirin, the protein binding of diclofenac is reduced, although the clearance of the free diclofenac sodium and misoprostol delayed-release tablets is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac sodium and aspirin is not generally recommended because of the potential risk of increased adverse effects.

Digoxin

Elevated digoxin levels have been reported in patients receiving digoxin and diclofenac sodium. Patients receiving digoxin and diclofenac sodium and misoprostol delayed-release tablets should be monitored for possible digoxin toxicity.

Warfarin:

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious bleeding greater than users of either drug alone.

Oral hypoglycemics:

Diclofenac sodium does not alter glucose metabolism in healthy people nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experience, of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac sodium that necessitated change in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac sodium may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Methotrexate:

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine:

Diclofenac sodium and misoprostol delayed-release tablets, like other NSAID containing products, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of diclofenac sodium and misoprostol delayed-release tablets may increase cyclosporine nephrotoxicity. Patients who begin taking diclofenac sodium and misoprostol delayed-release tablets or who increase their dose of diclofenac sodium and misoprostol delayed-release tablets while taking cyclosporine may develop toxicity characteristic for cyclosporine. They should be observed closely, particularly if renal function is impaired.

Lithium:

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Antacids:

Antacids reduce the bioavailability of misoprostol acid. Antacids may also delay absorption of diclofenac sodium. Magnesium-containing antacids exacerbate misoprostol-associated diarrhea. Thus, it is not recommended that diclofenac sodium and misoprostol delayed-release tablets be coadministered with magnesium-containing antacids.

Diuretics:

Clinical studies, as well as postmarketing observations, have shown that diclofenac sodium and misoprostol delayed-release tablets can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **WARNINGS, Renal Effects**), as well as to assure diuretic efficacy. Concomitant therapy with potassium-sparing diuretics may be associated with increased serum potassium levels.

CYP2C9 inhibitors

Use caution when dosing diclofenac with CYP2C9 inhibitors (e.g. voriconazole). Concomitant use of CYP2C9 inhibitors may enhance toxicity of diclofenac due to an increase in systemic exposure to diclofenac. When concomitant use of CYP2C9 inhibitors is necessary, the total daily dose of diclofenac should not exceed the lowest recommended dose of diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg twice daily (see DOSAGE AND ADMINISTRATION).

Voriconazole:

In a published study, 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 2.1-fold and 1.8- fold respectively when coadministered with voriconazole compared to diclofenac alone.

CYP2C9 inducers

Use caution when dosing diclofenac with CYP2C9 inducers (e.g. rifampin). Concomitant use of CYP2C9 inducers may lead to compromised efficacy due to a decrease in systemic exposure to diclofenac. The separate products of misoprostol and diclofenac should be used if a higher dose of diclofenac is deemed necessary (see **DOSAGE AND ADMINISTRATION**).

Other drugs:

In small groups of patients (7 to 10 patients/interaction study), the concomitant administration of acathiozine, gold, chloroquine, D-penicillamine, prednisolone, phenylbutazone or digitoxin did not significantly affect the peak levels and AUC levels of diclofenac sodium. Phenobarbital toxicity has been reported to have occurred in a patient on chronic phenobarbital treatment following the initiation of diclofenac therapy. *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.

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.

Carcinogenesis, mutagenesis, impairment of fertility

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 and misoprostol delayed-release tablets given alone. Diclofenac sodium and misoprostol delayed-release tablets themselves (diclofenac sodium and misoprostol combinations in 250/1 ratio) were 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 micronucleus test.

In a 24-month rat carcinogenicity study, oral misoprostol at doses up to 2.4 mg/kg/day (14.4 mg/ m^2/day; 24 times the recommended maximum human dose of 0.6 mg/ m^2/day) was not tumorigenic. In a 21-month mouse carcinogenicity study, oral misoprostol at doses up to 16 mg/kg/day (48 mg/ m^2/day), 80 times the recommended maximum human dose based on body surface area, was not tumorigenic. 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 recommended maximum human dose 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. These findings suggest the possibility of a general adverse effect on fertility in males and females.

In a 24-month rat carcinogenicity study, oral diclofenac sodium up to 2 mg/kg/day (12 mg/ m^2/day) was not tumorigenic. For a 50-kg person of average height (1.46 m^2 body surface area), this dose represents 0.08 times the recommended maximum human dose (148 mg/ m^2) on a body surface area basis. 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 recommended maximum human dose based on body surface area) in males and 1 mg/kg/day (3 mg/ m^2/day, 0.02 times the recommended maximum human dose based on body surface area) in females was not tumorigenic. Diclofenac sodium at oral doses up to 4 mg/ kg/day (24 mg/ m^2/day, 0.16 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Pregnancy category X: See boxed **CONTRAINDICATIONS AND WARNINGS** regarding misoprostol.

Non-teratogenic effects

See boxed **CONTRAINDICATIONS AND WARNINGS**. Misoprostol may endanger pregnancy (may cause abortion) and thereby cause harm to the fetus when administered to a pregnant woman. 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 genital bleeding, shock, fetal bradycardia, and fetal and maternal death have been reported. Higher doses of misoprostol, including the 100 mcg tablet, may increase the risk of complications from uterine hyperstimulation. Diclofenac sodium and misoprostol delayed-release tablets, which contain 200 mcg of misoprostol, are likely to have a greater risk of uterine hyperstimulation than the 100 mcg tablet of misoprostol. Abortions caused by misoprostol may be incomplete. 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.

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, fetal bradycardia, and pelvic pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Additionally, because of the known effects of nonsteroidal anti-inflammatory drugs including the diclofenac sodium component of diclofenac sodium and misoprostol delayed-release tablets, on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Teratogenic effects

See boxed **CONTRAINDICATIONS AND WARNINGS**. 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. 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.

An oral teratology study has been performed in pregnant rabbits at dose combinations (250:1 ratio) up to 10 mg/kg/day diclofenac sodium (120 mg/ m^2/day, 0.8 times the recommended maximum human dose based on body surface area) and 0.04 mg/kg/day misoprostol (0.48 mg/ m^2/day, 0.8 times the recommended maximum human dose based on body surface area) and has revealed no evidence of teratogenic potential for diclofenac sodium and misoprostol delayed-release tablets.

Oral teratology studies have been performed in pregnant rats at doses up to 1.6 mg/kg/ day (9.6 mg/ m^2/day, 16 times the recommended maximum human dose 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 recommended maximum human dose based on body surface area) and have revealed no evidence of teratogenic potential for misoprostol.

Oral teratology studies have been performed in pregnant mice at doses up to 20 mg/kg/ day (60 mg/m^2/day, 0.4 times the recommended maximum human dose based on body surface area), pregnant rats at doses up to 10 mg/kg/day (60 mg/ m^2/day, 0.4 times the recommended maximum human dose 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 recommended maximum human dose based on body surface area) and have revealed no evidence of teratogenic potential for diclofenac sodium.

However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nursing mothers

Diclofenac sodium has been found in the milk of nursing mothers. Misoprostol is rapidly metabolized in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. There are no published reports of adverse effects of misoprostol in breastfeeding infants of mothers taking misoprostol. Caution should be exercised when diclofenac sodium and misoprostol delayed-release tablets are administered to a nursing woman.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred.

Pediatric use

Safety and effectiveness of diclofenac sodium and misoprostol delayed-release tablets in pediatric patients have not been established.

Geriatric use

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older). Of the more than 2,100 subjects in clinical studies with diclofenac sodium and misoprostol delayed-release tablets, 25% were 65 and over, while 6% were 75 and over. In studies with diclofenac, 31% of subjects were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Diclofenac is known to be substantially excreted by the kidney, and the risk of toxic reactions to diclofenac sodium and misoprostol delayed-release tablets may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **WARNINGS—Renal Effects**).

Based on studies in the elderly, no adjustment of the dose of diclofenac sodium and misoprostol delayed-release tablets is necessary in the elderly for pharmacokinetic reasons (see *Pharmacokinetics of diclofenac sodium and misoprostol delayed-release tablets—Specific populations*), although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging.

ADVERSE REACTIONS

Adverse reactions associated with diclofenac sodium and misoprostol delayed-release tablets

Adverse reaction information for diclofenac sodium and misoprostol delayed-release tablets are derived from Phase III multinational controlled clinical trials in over 2,000 patients, receiving diclofenac sodium and misoprostol delayed-release tablets, 50/0.2 mg or diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg , as well as from blinded, controlled trials of Voltaren® Delayed-Release Tablets(diclofenac) and Cytotec® Tablets (misoprostol).

Gastrointestinal

GI disorders had the highest reported incidence of adverse events for patients receiving diclofenac sodium and misoprostol delayed-release tablets. These events were generally minor, but led to discontinuation of therapy in 9% of patients on diclofenac sodium and misoprostol delayed-release tablets and 5% of patients on diclofenac. For GI ulcer rates, see **CLINICAL STUDIES—Upper gastrointestinal safety**.

GI disorder	**Diclofenac sodium and misoprostol delayed-release tablets**	**Diclofenac**
Abdominal pain	21%	15%
Diarrhea	19%	11%
Dyspepsia	14%	11%
Nausea	11%	6%
Flatulence	9%	4%

Diclofenac sodium and misoprostol delayed-release tablets 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 and misoprostol delayed-release tablets is prescribed. The incidence of diarrhea can be minimized by administering diclofenac sodium and misoprostol delayed-release tablets 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 and misoprostol delayed-release tablets (see below). Postmenopausal vaginal bleeding may be related to administration of diclofenac sodium and misoprostol delayed-release tablets. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology (see boxed **CONTRAINDICATIONS AND WARNINGS**).

Elderly

Overall, there were no significant differences in the safety profile of diclofenac sodium and misoprostol delayed-release tablets in over 500 patients 65 years of age or older compared with younger patients.

Other adverse experiences reported occasionally or rarely with diclofenac sodium and misoprostol delayed-release tablets, diclofenac or other NSAIDs, or misoprostol are:

Body as a whole: Asthenia, death, fatigue, fever, infection, malaise, sepsis, chills.

Cardiovascular system: Arrhythmia, atrial fibrillation, congestive heart failure, hypertension, hypotension, increased CPK, increased LDH, myocardial infarction, palpitations, phlebitis, premature ventricular contractions, syncope, tachycardia, vasculitis.

Central and peripheral nervous system: Coma, convulsions, dizziness, drowsiness, headache, hyperesthesia, hypertonia, hypesthesia, insomnia, meningitis, migraine, neuralgia, paresthesia, somnolence, stroke, tremor, vertigo.

Digestive: Anorexia, appetite changes, constipation, dry mouth, dysphagia, enteritis, esophageal ulceration, esophagitis, eructation, gastritis, gastroesophageal reflux, GI bleeding, GI neoplasm benign, glossitis, heartburn, hematemesis, hemorrhoids, intestinal perforation, peptic ulcer, stomatitis and ulcerative stomatitis, tenesmus, vomiting.

Female reproductive disorders: Breast pain, dysmenorrhea, intermenstrual bleeding, leukorrhea, menstrual disorder, menorrhagia, vaginal hemorrhage.

Hemic and lymphatic system: Agranulocytosis, anemia, aplastic anemia, coagulation time increased, ecchymosis, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, lymphadenopathy, melena, pancytopenia, pulmonary embolism, purpura, rectal bleeding, thrombocytopenia, thrombocytopenia.

Hypersensitivity: Angioedema, laryngeal/pharyngeal edema, urticaria.

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

Male reproductive disorders: Impotence, perineal pain.

Metabolic and nutritional: Alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, BUN increased, dehydration, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, hyponatremia, interstitial edema, porphyria, weight changes.

Musculoskeletal system: Arthralgia, myalgia.

Psychiatric: Anxiety, concentration impaired, confusion, depression, disorientation, dream abnormalities, hallucinations, irritability, nervousness, paranoia, psychotic reaction.

Respiratory system: Asthma, coughing, dyspnea, hyperventilation, pneumonia, respiratory depression

Skin and appendages: Acne, alopecia, bruising, eczema, erythema multiforme, exfoliative dermatitis, pemphigoid reaction, photosensitivity, pruritus, pruritus ani, rash, skin ulceration, Stevens-Johnson syndrome, sweating increased, toxic epidermal necrolysis.

Special senses: Hearing impairment, taste loss, taste perversion, tinnitus.

Urinary system: Cystitis, dysuria, hematuria, interstitial nephritis, micturition frequency, nocturia, nephrotic syndrome, oliguria/polyuria, papillary necrosis, proteinuria, renal failure, urinary tract infection.

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

OVERDOSAGE

The toxic dose of diclofenac sodium and misoprostol delayed-release tablets has not been determined. However, signs of overdosage from the components of the product have been described.

Diclofenac sodium

Clinical signs that may suggest diclofenac sodium overdose include GI complaints, confusion, drowsiness or general hypotonia. Reports of overdosage with diclofenac cover 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5.0 g in a 17-year-old man who suffered loss of consciousness, increased intracranial pressure, and aspiration pneumonitis, and died 2 days after overdose. A 24-year-old woman who took 4.0 g and the 29- and 42-year-old women, each of whom took 3.75 g, did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old woman who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal studies show a wide range of susceptibilities to acute overdosage, with primates being more resistant to acute toxicity than rodents (LD50 in mg/kg: rats, 55; dogs, 500; monkeys, 3500).

Misoprostol

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. In animals, the acute toxic effects are diarrhea, GI lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia.

DICLOFENAC SODIUM AND MISOPROSTOL DELAYED-RELEASE TABLETS

Symptoms of overdosage with diclofenac sodium and misoprostol delayed-release tablets should be treated with supportive therapy. In case of acute overdosage, gastric lavage is recommended. 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. The use of oral activated charcoal may help to reduce the absorption of diclofenac sodium and misoprostol.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of diclofenac sodium and misoprostol delayed-release tablets and other treatment options before deciding to use diclofenac sodium and misoprostol delayed-release tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

After observing the response to initial therapy with diclofenac sodium and misoprostol delayed-release tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of rheumatoid arthritis and osteoarthritis the recommended dose is given below.

Diclofenac sodium and misoprostol delayed-release tablets are administered as diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg (50 mg diclofenac sodium/200 mcg misoprostol) or as diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg (75 mg diclofenac sodium/200 mcg misoprostol).

Note: See **SPECIAL DOSING CONSIDERATIONS** section, below.

Osteoarthritis: The recommended dosage for maximal GI mucosal protection is diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg tid. For patients who experience intolerance, diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg bid or diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg bid can be used, but are less effective in preventing ulcers. This fixed combination product, diclofenac sodium and misoprostol delayed-release tablets, is not recommended for patients who would not receive the appropriate dose of both ingredients. Doses of the components delivered with these regimens are as follows:

	OA regimen	**Diclofenac sodium (mg/day)**	**Misoprostol (mcg/day)**
Diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg	tid	150	600
	bid	100	400
Diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg	bid	150	400

Rheumatoid Arthritis: The recommended dosage is diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg tid or qid. For patients who experience intolerance, diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg bid or diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg bid can be used, but are less effective in preventing ulcers. This fixed combination product, diclofenac sodium and misoprostol delayed-release tablets, is not recommended for patients who would not receive the appropriate dose of both ingredients. Doses of the components delivered with these regimens are as follows:

	RA regimen	**Diclofenac sodium (mg/day)**	**Misoprostol (mcg/day)**
Diclofenac sodium and misoprostol delayed-release tablets 50/0.2 mg	qid	200	800
	tid	150	600
	bid	100	400
Diclofenac sodium and misoprostol delayed-release tablets 75/0.2 mg	bid	150	400

SPECIAL DOSING CONSIDERATIONS: Diclofenac sodium and misoprostol delayed-release tablets contain misoprostol, which provides protection against gastric and duodenal ulcers (see **CLINICAL STUDIES**). For gastric ulcer prevention, the 200 mcg qid and tid regimens are therapeutically equivalent, but more protective than the bid regimen. For duodenal ulcer prevention, the qid regimen is more protective than the tid or bid regimens. However, the qid regimen is less well tolerated than the tid regimen because of usually self-limited diarrhea related to the misoprostol dose (see **ADVERSE REACTIONS— Gastrointestinal**), and the bid regimen may be better tolerated than tid in some patients.

Dosages may be individualized using the separate products (misoprostol and diclofenac), after which the patient may be changed to the appropriate dose of diclofenac sodium and misoprostol delayed-release tablets. If clinically indicated, misoprostol co-therapy with diclofenac sodium and misoprostol delayed-release tablets, or use of the individual components to optimize the misoprostol dose and/or frequency of administration, may be appropriate. The total dose of misoprostol should not exceed 800 mcg/day, and no more than 200 mcg of misoprostol should be administered at any one time. Doses of diclofenac greater than 150 mg/day in osteoarthritis or higher than 225 mg/day in rheumatoid arthritis are not recommended.

For additional information, it may be helpful to refer to the package inserts for misoprostol immediate release tablets and diclofenac sodium delayed release tablets.

HOW SUPPLIED

Diclofenac sodium and misoprostol delayed-release tablets (diclofenac sodium/misoprostol) are supplied as a film-coated tablet in dosage strengths of either 50 mg diclofenac sodium/200 mcg misoprostol or 75 mg diclofenac sodium/200 mcg misoprostol. The 50 mg/200 mcg dosage strength is a white circular, biconvex tablets with off white circular enteric coated inlay tablets on one side and debossed "DM2" on other side. The 75 mg/200 mcg dosage strength is a white circular, biconvex tablets with off white circular enteric coated inlay tablets on one side and debossed "DM1" on other side.

The dosage strengths are supplied in:

Strength	NDC Number	Size
50/200	42367-110-06	bottle of 60
	42367-110-09	bottle of 90
75/200	42367-111-06	bottle of 60

Store at or below 25°C (77°F), in a dry area.

Rx only

Manufactured by: Cipla Ltd., India

For: Eagle Pharmaceuticals, Inc.
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