Miclofenac®

COMPOSITION

Miclofenac® 50: Each tablet consists of an enteric-coated core containing 50 mg Diclofenac sodium BP surrounded by an outer mantle containing 200 mcg Misoprostol INN.
Miclofenac® 75: Each tablet consists of an enteric-coated core containing 75 mg Diclofenac sodium BP surrounded by an outer mantle containing 200 mcg Misoprostol INN.

PHARMACOLOGY

This combination product contains Diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, and Misoprostol, a gastrointestinal (GI) mucosal protective prostaglandin E1 analog.
Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacological 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. Diclofenac sodium in this combination 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 1–4 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.
Misoprostol is a synthetic prostaglandin E1 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 prevent gastric and duodenal ulcers is the result of its antisecretory effect, its mucosal protective effect, or both. Orally administered misoprostol is rapidly and extensively absorbed, and it undergoes rapid metabolism to its biologically active metabolite, misoprostol acid. Misoprostol acid in this combination reaches a maximum plasma concentration in about 20 minutes and is, thereafter, quickly eliminated with an elimination half life 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.

INDICATION

It is 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.

DOSAGE AND ADMINISTRATION

Osteoarthritis: For maximal GI mucosal protection the recommended dosage is **Miclofenac®** 50 tid. For patients who experience intolerance, **Miclofenac®** 50 or **Miclofenac®** 75 bid can be used.

Rheumatoid Arthritis: For maximal GI mucosal protection the recommended dosage is **Miclofenac®** 50 tid or qid. For patients who experience intolerance, **Miclofenac®** 50 or **Miclofenac®** 75 bid can be used.

Special Dosing Considerations: This preparation contains misoprostol, which provides protection against gastric and duodenal ulcers. 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 and the bid regimen may be better tolerated than tid in some patients.

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 higher than 150 mg/day in osteoarthritis or higher than 225 mg/day in rheumatoid arthritis are not recommended.

ADVERSE EFFECTS

Gastrointestinal: GI disorders had the highest reported incidence of adverse events for patients receiving this preparation. It can cause more abdominal pain, diarrhea and other GI symptoms than diclofenac alone. The incidence of diarrhea can be minimized by administering it 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 this preparation. Postmenopausal vaginal bleeding may be related to its administration.

CONTRAINDICATIONS AND PRECAUTION

It is contraindicated in patients with hypersensitivity to diclofenac or to misoprostol or other prostaglandins. It 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.

DRUG INTERACTIONS

Aspirin: Concomitant administration of this preparation and aspirin is not recommended because diclofenac sodium is displaced from its binding sites by aspirin, resulting in lower plasma concentrations, peak plasma levels and AUC values. *Digoxin:* Elevated digoxin levels have been reported in patients receiving digoxin and diclofenac sodium. Patients receiving digoxin and this preparation should be monitored for possible digoxin toxicity. *Antihypertensive agents:* NSAIDs can inhibit the activity of antihypertensives, including ACE inhibitors. Thus, caution should be taken when administering this preparation with such agents. *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. Physicians should consider the

possibility that diclofenac sodium may alter a diabetic patient's response to insulin or oral hypoglycemic agents. *Methotrexate and cyclosporine:* This preparation may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of this preparation may increase serum concentrations of methotrexate and increase cyclosporine nephrotoxicity. Patients who begin taking this preparation or who increase their dose of this preparation or any other NSAID containing product while taking methotrexate or cyclosporine may develop toxicity characteristic for these drugs. 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 this preparation be coadministered with magnesium-containing antacids. *Diuretics:* The diclofenac sodium component of this preparation, like other NSAIDs, can inhibit the activity of diuretics. Concomitant therapy with potassium-sparing diuretics may be associated with increased serum potassium levels.

USE IN PREGNANCY AND LACTATION

Because of the abortifacient property of the misoprostol component, it is contraindicated in women who are pregnant. It 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.

In such patients, It 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 it only on the second or third day of the next normal menstrual period

Diclofenac sodium has been found in the milk of nursing mothers. It is unlikely that misoprostol is excreted into milk since the drug is rapidly metabolized throughout the body. Excretion of the active metabolite (misoprostol acid) into milk is possible, but has not been studied. Because of the potential for serious adverse reactions in nursing infants, it is not recommended for use by nursing mothers.

STORAGE

Store at cool and dry place, protect from light and moisture. Keep out of the reach of children.

HOW SUPPLIED

Miclofenac® 50: Box containing 3 x 10's tablet in blister pack.
Miclofenac® 75: Box containing 3 x 10's tablet in blister pack.