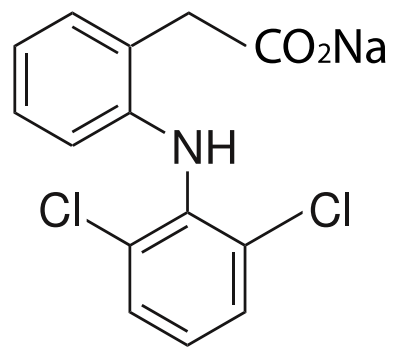
Dimis®
(Diclofenac Sodium / Misoprostol)
Delayed-release Tablets U.S.P.

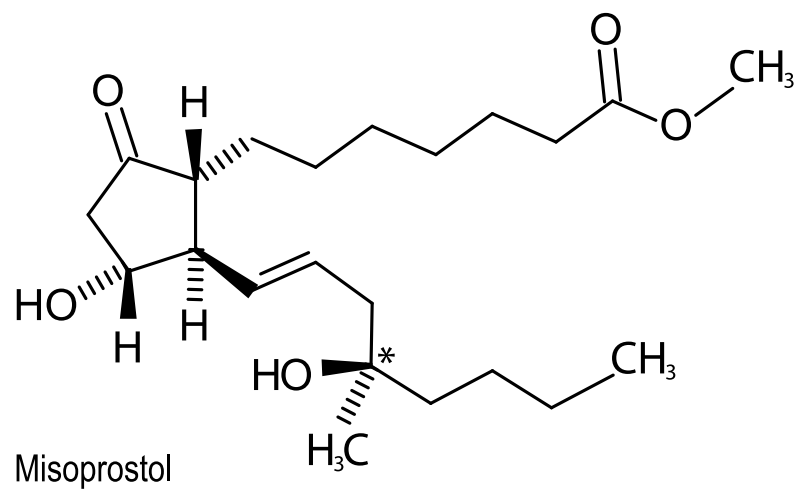
50mg/200mcg
75mg/200mcg

ڈائمِس
۵۰ ملی گرام/ ۲۰۰ مائیکروگرام
۷۵ ملی گرام/ ۲۰۰ مائیکروگرام

(ڈائیکلوفینک سوڈیم / میزوپروسٹول) ٹیبلٹس یو۔ایس۔پی۔

DESCRIPTION: Dimis® (Diclofenac Sodium/Misoprostol) is a combination product containing diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, and misoprostol, a gastrointestinal (GI) mucosal protective prostaglandin E1 analog. Dimis® tablets consist of an enteric-coated core containing Diclofenac Sodium surrounded by an outer mantle containing Misoprostol. Its chemical formula and name are: Diclofenac Sodium ($C_{14}H_{10}Cl_2NO_2Na$) [M.W. = 318.14] 2-[(2,6- dichloro-phenyl) amino] benzeneacetic acid, monosodium salt. Misoprostol ($C_{22}H_{38}O_5$) [M.W. = 382.54] (±) methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.





Misoprostol

Dimis® Delayed-release Tablets U.S.P. 50mg/200mcg Dimis® Delayed-release Tablets 75mg/200mcg tablets:

COMPOSITION:
Each tablet contains:
Gastro-resistant core of
Diclofenac Sodium B.P. 50mg
Misoprostol U.S.P. 200mcg
(outer mantle)

COMPOSITION:
Each tablet contains:
Gastro-resistant core of
Diclofenac Sodium B.P. 75mg
Misoprostol U.S.P. 200mcg
(outer mantle)

CLINICAL PHARMACOLOGY

Pharmacodynamics and pharmacokinetics of Diclofenac Sodium: Diclofenac Sodium/Misoprostol 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. Only 50% of the absorbed dose is systematically available. Peak plasma levels are achieved in 2 hours (range 1–4 hours). 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.

Pharmacodynamics and pharmacokinetics of Misoprostol: 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 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: Misopros-

tol, over the range of 50–200 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. Misoprostol acid in Dimis® reaches a maximum plasma concentration in about 20 minutes and is, thereafter, quickly eliminated with an elimination t1/2 of about 30 minutes. 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.

INDICATIONS:

Dimis® 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.

Contraindications and Warnings:

Dimis®. Contains 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. Dimis® should not be taken by pregnant women. Patients must be advised of the abortifacient property and warned not to give the drug to others. Dimis® 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.

PREGNANCY:

Pregnancy category X: Nursing mothers: Diclofenac sodium has been found in the milk of nursing mothers. Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. Dimis® should not be administered to nursing mothers. Pediatric use: Safety & effectiveness of Dimis® in pediatric patients have not been established. Geriatric use: No adjustment of the dose of Dimis® is necessary in the elderly. Cardiovascular Risk: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal.

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.

HYPERSENSITIVITY:

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

PRECAUTIONS:

General: Dimis® cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency.

Hematological Effects: Anemia is sometimes seen in patients receiving NSAIDs, including Dimis®. this may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis.

Pre-existing Asthma: Patients with asthma may have aspirin-sensitive asthma. Cross reactivity, including bronchospasm, between aspirin and other NSAID has been reported in such aspirin-sensitive patients, Dimis® should not be administered to patients with this form of aspirin sensitivity. Aseptic meningitis: As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. Porphyria: The use of Dimis® in patients with hepatic porphyria should

be avoided.
Drug Interactions: ACE-Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors.
Aspirin: When Dimis® is administered with aspirin, the protein binding of diclofenac is reduced, although the clearance of the free Dimis® is not altered.
Digoxin: Elevated digoxin levels have been reported in patients receiving digoxin and diclofenac sodium.
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.
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.
Cyclosporine: Dimis®, like other NSAID containing products, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of Dimis® may increase cyclosporine nephrotoxicity.
Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance.
Antacids: Antacids reduce the bioavailability of misoprostol acid. Antacids may also delay absorption of diclofenac sodium. Magnesium containing antacids exacerbate misoprostol associated diarrhea. **Diuretics:** Dimis® can reduce the natriuretic effect of furosemide and thiazides in some patients.

ADVERSE EFFECTS:

Gastrointestinal Effects: (Risk of Ulceration, Bleeding and Perforation) NSAIDs, including Dimis®, 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 3-6 months, and in about 2-4% 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.
Cardiovascular Thrombotic Effects: 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 ef-

fective 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. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events. Hypertension: NSAIDs, including Dimis®, can lead to onset of new hypertension or worsening of pre existing 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 Dimis®, 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. Dimis® should be used with caution in patients with fluid retention or heart failure.

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 maintanance 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.

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

Anaphylactoid Reactions: As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Dimis®. Dimis® 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. Emergency help should be sought in cases where an anaphylactoid reaction occurs. Allergic reactions have been reported by less than 0.1% of patients in clinical trials, and there have been rare reports of anaphylaxis. Skin Reactions: NSAIDs, including Dimis®, 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

OVERDOSAGE:

The toxic dose of Dimis®. 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.

Misoprostol: The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600mcg have been tolerated, with only symptoms of GI discomfort being reported. Symptoms of overdosage with Dimis® 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:

Osteoarthritis: The recommended dosage for maximal GI mucosal protection is DIMIS® 50mg/200mcg tid. For patients who experience intolerance, DIMIS® 75mg/200mcg bid or DIMIS® 50mg/200mcg bid can be used, but are less effective in preventing ulcers. This fixed combination product, DIMIS® is not appropriate for patients who would not receive the appropriate dose of both ingredients Rheumatoid Arthritis: The recommended dosage is DIMIS® 50mg/200mcg tid or qid. For patients who experience intolerance, DIMIS® 75mg/200mcg bid or DIMIS® 50mg/200mcg bid can be used, but are less effective in preventing ulcers. This fixed combination product, DIMIS®, is not appropriate for patients who would not receive the appropriate dose of both ingredients

DOSAGE:

As directed by the physician.

INSTRUCTIONS:

Store below 30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of children.

PRESENTATION:

Dimis 50mg/200mcg Delayed-release tablets U.S.P. are available in 20's Alu-Alu blister pack.
Dimis 75mg/200mcg Delayed-release tablets U.S.P. are available in 20's Alu-Alu blister pack.

خوراک : معالج کی ہدایت کے مطابق استعمال کریں۔
ہدایات : ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔

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ISO 9001:2015 ISO 14001:2015 ISO 45001:2018

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