CYTOPAN™ 50
CYTOPAN™ 75

[Diclofenac Sodium + Misoprostol]

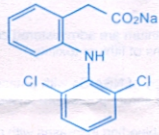
50mg + 200mcg, 75mg + 200mcg
Tablets

سائیٹوپان ۵۰
سائیٹوپان ۷۵

DESCRIPTION

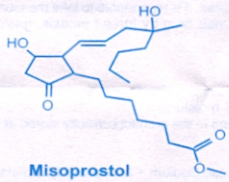
CYTOPAN 50 & CYTOPAN 75 are combination products containing diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, and misoprostol, a gastrointestinal (GI) mucosal protective prostaglandin E_1 analog.

Diclofenac sodium a phenylacetic acid derivative is chemically described as 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt. Its molecular formula is $C_{14}H_{10}Cl_2NO_2Na$ and the structural formula is:



Diclofenac Sodium

Misoprostol is a synthetic, oral prostaglandin E_1 analog. Chemically it is described as (±) methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate. The molecular formula is $C_{22}H_{38}O_5$ and the structural formula is:



Misoprostol

QUALITATIVE & QUANTITATIVE COMPOSITION

CYTOPAN (Diclofenac Sodium+Misoprostol) is available for oral administration as:

1. CYTOPAN 50 Tablets
   Each tablet contains:
   Diclofenac Sodium BP... 50mg
   Misoprostol... 200mcg

2. CYTOPAN 75 Tablets
   Each tablet contains:
   Diclofenac Sodium BP... 75mg
   Misoprostol... 200mcg

CLINICAL PHARMACOLOGY

Mechanism of Action

Diclofenac Sodium

The mechanism of action of diclofenac sodium, like other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Misoprostol

It inhibits basal and nocturnal gastric acid secretion through a direct action on the parietal cell. Misoprostol also exerts a mucosal protectant effect that may contribute to its effectiveness in treating ulcers.

Pharmacokinetics

Diclofenac Sodium

Absorption: Diclofenac sodium, orally administered, is completely absorbed from the GI tract after fasting. The enteric-coated formulation of diclofenac sodium 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.

Distribution: Diclofenac sodium is extensively & reversibly bound (99%) to serum albumin. Diclofenac sodium penetrates synovial fluid where T_{max} occurs 2 to 4 hours after plasma T_{max}. The synovial fluid elimination half-life is at least 3 times greater than that for plasma. Diclofenac sodium is distributed into breast milk but the amount is considered to be too small to be harmful to a breastfed infants. The apparent volume of distribution is 0.12 to 0.17l/kg.

Metabolism: Diclofenac sodium undergoes first pass metabolism producing derivatives of diclofenac sodium. These phenolic metabolites are largely inactive, and (along with the parent compound) are mostly converted to glucuronide conjugates.

Elimination: In humans about 65% of the drug and its metabolites are eliminated in the urine and the balance through bile in the feces. About 1% of an oral dose is excreted unchanged in urine. The mean terminal drug half-life in plasma is 2 hours after oral doses.

Misoprostol

Absorption: Orally administered misoprostol is rapidly and extensively (88%) absorbed. Food and antacids decrease the rate and extent of absorption.

Distribution: Misoprostol distribution has not been fully elucidated. It is unknown whether this agent crosses the placenta or is distributed into breast milk but because it can stimulate uterine contractions, it should not be used during pregnancy.

Metabolism: The drug undergoes extensive first-pass metabolism to form the principal and active metabolite misoprostol acid. Portion of this metabolism occurs in the parietal cell. Misoprostol acid is further metabolized in the body tissues.

Elimination: The elimination half-life of misoprostol acid is between 20 - 40 minutes, but it can be up to 80 minutes in those with renal impairment. Less than 1% of a dose is excreted in the urine as unchanged drug. Approximately 15% of a dose is excreted in the feces, with 74% being excreted in the urine within 7 days.

THERAPEUTIC INDICATIONS

CYTOPAN 50 (Diclofenac Sodium+Misoprostol) & CYTOPAN 75 (Diclofenac Sodium+Misoprostol) are indicated for acute and chronic treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute musculoskeletal disorders.

The misoprostol component of CYTOPAN 50 & CYTOPAN 75 is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including Aspirin) induced gastric and duodenal ulcers.

DOSAGE AND ADMINISTRATION

Osteoarthritis:

The recommended dosage for maximal GI mucosal protection is CYTOPAN 50 (Diclofenac Sodium+Misoprostol) tablets t.i.d. For patients who experience intolerance, CYTOPAN 75 (Diclofenac Sodium+Misoprostol) tablets b.i.d or CYTOPAN 50 (Diclofenac Sodium+Misoprostol) tablets b.i.d can be used, but are less effective in preventing ulcers.

Rheumatoid Arthritis:

The recommended dosage is CYTOPAN 50 (Diclofenac Sodium+Misoprostol) tablets t.i.d or q.i.d. For patients who experience intolerance, CYTOPAN 75 (Diclofenac Sodium + Misoprostol) tablets b.i.d or CYTOPAN 50 (Diclofenac Sodium+Misoprostol) tablets b.i.d can be used, but are less effective in preventing ulcers.

Ankylosing Spondylitis:

The recommended dosage is CYTOPAN 50 (Diclofenac Sodium+Misoprostol) tablets t.i.d or q.i.d.

Acute Musculoskeletal Disorders:

The recommended dosage for maximal GI mucosal protection is CYTOPAN 50 (Diclofenac Sodium+Misoprostol) tablets b.i.d or t.i.d.

Special Dosing Considerations:

CYTOPAN 50 & CYTOPAN 75 contains misoprostol, which provides protection against gastric and duodenal ulcers. For gastric ulcer prevention, the 200mcg q.i.d and t.i.d regimens are therapeutically equivalent but more protective than the b.i.d regimen.

For duodenal ulcer prevention, the q.i.d regimen is more protective than the t.i.d or b.i.d regimens. However, the q.i.d regimen is less well tolerated than the t.i.d regimen and the b.i.d regimen may be better tolerated than t.i.d in some patients.

Note: The total dose of misoprostol should not exceed 800mcg/day and no more than 200mcg of misoprostol should be administered at any one time. Doses of diclofenac sodium higher than 150mg/day in osteoarthritis or higher than 225mg/day in rheumatoid arthritis are not recommended.

ADVERSE REACTIONS

The most common adverse reactions encountered with NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. The following adverse reactions occurred:

Gastrointestinal: abdomen enlarged, esophageal ulceration, gall bladder disorder, glossitis, hematemesis, hiccup and melena.
CNS/Psychiatric: anorexia, anxiety, concentration impaired, depression, hypoesthesia, dry mouth, speech disorder and vertigo.
Dermatologic: angioedema, erythema multiforme, sweating increased and urticaria.
Cardiovascular: palpitation and syncope.
Special Senses: earache, eye pain, taste loss, taste abnormalities, tinnitus and vision abnormal.
Hematologic: leukopenia and thrombocytopenia.
Hepatic: bilirubinemia, abnormal hepatic function, LDH increased, and alkaline phosphatase increased.
Metabolic: BUN increased and glycosuria.
Respiratory: hyperventilation and sputum increased.
Gynecological: menstrual disorder, intermenstrual bleeding, dysmenorrhea, leukorrhea, and vaginal bleeding.
Body as a Whole: hot flushes, malaise and rigors.
Urinary: dysuria, abnormal urine, hematuria and cystitis.

CONTRAINDICATIONS

Diclofenac Sodium+misoprostol combination is contraindicated in:

- patients with hypersensitivity to diclofenac sodium or to misoprostol or other prostaglandins.

- pregnant women, because its misoprostol component can cause abortion.
- patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.
- patients having advanced kidney disease.
- combination with aspirin and magnesium containing antacids.
- patients with active liver disease.
- lactating patients.
- Patients with active peptic ulcer/haemorrhage or perforation or who have active GI bleeding or other active bleedings e.g. cerebrovascular bleedings.
- Treatment of peri-operative pain in the setting of coronary bypass graft (CABG) surgery.
- Patients with severe heart failure.

WARNINGS

Special note for women: Because of the abortifacient property of misoprostol CYTOPAN 50 & CYTOPAN 75 are contraindicated for use by pregnant women. Misoprostol may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by misoprostol may be incomplete, which could lead to dangerous bleeding, hospitalization, surgery, infertility or maternal or fetal death.
Patients must be advised of the abortifacient property and warned not to give the drug to others.

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.

Childbearing Potential
Diclofenac sodium+misoprostol combination 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.

Gastrointestinal Effects-Risk of GI Ulceration, Bleeding and Perforation
Serious GI toxicity, such as inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy.
Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms and the steps to take if they occur.
NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or GI bleeding.

PRECAUTIONS

General: Diclofenac sodium+misoprostol combination cannot be used to substitute for corticosteroids or to treat for 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.

Use in pre menopausal women: Diclofenac sodium+misoprostol combination should not be used in pre-menopausal women unless they use effective contraception.

Skin reactions: Serious skin reactions have been reported very rarely in association with the use of NSAIDs, including diclofenac sodium+misoprostol combination. Diclofenac sodium+misoprostol combination should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Renal effects: Caution should be used when initiating treatment in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with diclofenac sodium+misoprostol combination.

Hepatic effects: Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms.
As with other NSAID containing products, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc), diclofenac sodium+misoprostol combination should be discontinued immediately.

Hematologic effects: Patients on long-term treatment with NSAIDs, including diclofenac sodium+misoprostol combination should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
Patients receiving diclofenac sodium+misoprostol combination who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants should be carefully monitored.

Fluid retention and edema: As with other NSAID containing products, diclofenac sodium+misoprostol combination should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Pre-existing asthma: Diclofenac sodium+misoprostol combination should be used with caution in patients with pre-existing asthma.

Geriatric use: No adjustment of the dose of diclofenac sodium+misoprostol combination is necessary in the elderly for pharmacokinetic reasons although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging.

Drug Interactions
Digoxin: Patients receiving digoxin with diclofenac sodium+misoprostol combination should be monitored for possible digoxin toxicity.

Antihypertensive agents: NSAIDs can inhibit the activity of anti-hypertensives, including ACE inhibitors. Thus, caution should be taken when administering this 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: Marketing experiences reports, changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac sodium that necessitated changes in the doses of such agents.

Methotrexate and Cyclosporine: Diclofenac sodium+misoprostol combination may increase serum concentrations of methotrexate and increase cyclosporine nephrotoxicity.

Lithium: When NSAIDs and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

Diuretics: Concomitant therapy of NSAIDs with potassium-sparing diuretics may be associated with increased serum potassium levels.

SSRI: Risk of gastrointestinal bleeding increases with concomitant use of NSAIDS with SSRI's.

OVERDOSAGE

Intensification of the pharmacological effects may occur with overdosage. Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. It is reasonable to take measures to reduce absorption of any recently consumed drug by forced emesis, gastric lavage or activated charcoal.

STORAGE

Store at 25°C (Excursions permitted between 15°C-30°C).
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

CYTOPAN 50 (Diclofenac Sodium + Misoprostol) Tablets are available in blister pack of 20's.

CYTOPAN 75 (Diclofenac Sodium + Misoprostol) Tablets are available in blister pack of 20's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
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