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Artisol-M Tablet

(Diclofenac sodium + Misoprostol)

آرتیسول-ایم ٹیبلٹ
(ڈیکلوفینک سڈیم + میسوپروستول)

COMPOSITION

Artisol-M Tablet 75mg/200mcg

Each tablet contains

Diclofenac sodium (Enteric coated core).....75mg
Misoprostol (Outer mantle).....200mcg

(USP Specification)

Diclosol-M Tablet 50mg/200mcg

Each tablet contains:

Diclofenac Sodium (Enteric coated Core).....50mg
Misoprostol (Outer mantle).....200mcg

(USP Specification)

DESCRIPTION

ARTISOL-M (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.

MECHANISM OF ACTION

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

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

Misoprostol is a synthetic prostaglandin E₁ analog with gastric anti-secretory and mucosal protective properties. NSAIDs inhibit prostaglandin synthesis. A deficiency of prostaglandins within the gastric and duodenal mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by NSAIDs. Misoprostol can increase bicarbonate and mucus production, but in humans this has been shown at doses 200 mcg and above that are also anti-secretory. 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 anti-secretory effect, its mucosal protective effect, or both.

INDICATIONS

ARTISOL-M 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.

DOSE & ADMINISTRATION

One tablet to be taken two or three times daily. Tablets should be swallowed whole, not chewed.

Elderly, renal, cardiac and hepatic impairment

No adjustment of dosage is necessary in the elderly or in

patients with hepatic impairment or mild to moderate renal impairment as pharmacokinetics are not altered to any clinically relevant extent. Nevertheless, elderly patients and patients with renal, cardiac or hepatic impairment should be closely monitored.

Pediatric population

The safety and efficacy of ARTISOL-M in children under 18 years has not been established.

PHARMACODYNAMICS

ARTISOL-M is a non-steroidal, anti-inflammatory drug, which is effective in treating the signs and symptoms of arthritic conditions.

This activity is due to the presence of diclofenac, which has been shown to have anti-inflammatory and analgesic properties. ARTISOL-M also contains the gastroduodenal mucosal protective component misoprostol, which is a synthetic prostaglandin E₁ analogue that enhances several of the factors that maintain gastroduodenal mucosal integrity.

PHARMACOKINETICS

Absorption

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

Misoprostol: Misoprostol is rapidly absorbed following oral administration of ARTISOL-M, and misoprostol acid (active metabolite) reaches a maximum plasma concentration in approximately 20 minutes. Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food, and total availability of misoprostol acid is reduced by use of concomitant antacid. Food decreases the multiple-dose bioavailability profile of ARTISOL-M.

Distribution

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

Misoprostol: The plasma protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range. After a single oral dose of misoprostol to nursing mothers, misoprostol acid was excreted in breast milk. The maximum concentration of misoprostol acid in expressed breast milk was achieved within 1 hour after

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

Metabolism

Diclofenac: Diclofenac metabolism is predominantly mediated via CYP2C9 in the liver. Five metabolites (4'-hydroxy-, 5'-hydroxy-, 3'-hydroxy-, 4',5'-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac) have been identified. The major metabolite (4'-hydroxy-diclofenac) has very weak pharmacologic activity. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acyl glucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy-diclofenac.

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

Excretion

Diclofenac: Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine and 35% in the bile. The elimination half-life of diclofenac is approximately 2 hours. The clearance of diclofenac is approximately 350 mL/min (equivalent to 21 L/h). Conjugates of unchanged diclofenac account for 5–10% 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 20–30% of the dose excreted in the urine and for 10–20% of the dose excreted in the bile. Conjugates of three other metabolites together account for 10–20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life = 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

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

WARNINGS AND PRECAUTIONS

The use of diclofenac/misoprostol with concomitant systemic NSAIDs including COX-2 inhibitors should be avoided, except for patients requiring low dose acetylsalicylic acid, caution is advised in such patients with close monitoring. Concomitant use of a systemic NSAID and another systemic NSAID may increase frequency of gastrointestinal ulcers and bleeding.

Renal/cardiac/hepatic impairment

In patients with renal, cardiac or hepatic impairment and in the elderly, caution is required since the use of NSAIDs may result in deterioration of renal function. In the following conditions ARTISOL-M should be used only in exceptional circumstances and with close clinical monitoring: advanced liver disease, severe dehydration.

Blood system/gastrointestinal

NSAIDs, including diclofenac/misoprostol, 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. When GI bleeding or ulceration occurs in patients receiving diclofenac/misoprostol, the treatment should be withdrawn. These events can occur at any time during treatment, with or without warning symptoms or in patients with a previous history of serious GI events.

ARTISOL-M in common with other NSAIDs, may decrease platelet aggregation and prolong bleeding time. Extra supervision is recommended in hematopoietic disorders or in conditions with defective coagulation or in patients with a history of cerebrovascular bleeding. Caution is required in patients suffering from ulcerative colitis or Crohn's Disease as these conditions may be exacerbated. Care should be taken in elderly patients and in patients treated with corticosteroids, other NSAIDs, or anti-coagulants.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including diclofenac/misoprostol. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Diclofenac/misoprostol should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hypersensitivity

NSAIDs may precipitate bronchospasm in patients suffering from, or with a history of bronchial asthma or allergic disease. As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

Long-term treatment

All patients who are receiving long-term treatment with NSAIDs should be monitored as a precautionary measure (e.g. renal, hepatic function and blood counts). During long-term, high dose treatment with analgesic/anti-inflammatory drugs, headaches can occur which must not be treated with higher doses of the medicinal product.

• ARTISOL-M may mask fever and thus an underlying infection.

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• Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

In women of childbearing potential

ARTISOL-M must not be used unless they use effective contraception and have been advised of the risks of taking the product if pregnant.

The label will state: 'Not for use in women of childbearing potential unless using effective contraception.'

SIDE EFFECTS

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

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, hyperesthesia, hypertonia, hypoesthesia, meningitis, migraine, neuralgia, somnolence, stroke, tremor.

Congenital, familial and genetic disorders: birth defects.

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

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

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

Hypersensitivity: angioedema, laryngeal/pharyngeal edema, urticaria.

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

Male reproductive disorders: impotence, perineal pain.

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

Pregnancy, puerperium and perinatal conditions: abnormal uterine contractions, uterine rupture/perforation, retained placenta, amniotic fluid embolism, incomplete abortion, premature birth, fetal death.

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

Reproductive system and breast disorders: female fertility decreased.

Respiratory system: dyspnea, pneumonia, respiratory depression.

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

Special senses: hearing impairment, taste loss.

Renal and urinary disorders: cystitis, hematuria, interstitial

nephritis, micturition frequency, nephrotic syndrome, oliguria, papillary necrosis, renal failure, glomerulonephritis membranous, glomerulonephritis minimal lesion, glomerulonephritis.

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

DRUG INTERACTIONS

• NSAIDs may attenuate the natriuretic efficacy of diuretics due to inhibition of intra-renal synthesis of prostaglandins. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels; hence serum potassium should be monitored.

• Because of their effect on renal prostaglandins, NSAIDs such as diclofenac may increase the nephrotoxicity of cyclosporin. When co-administered with cyclosporin, there is a two-fold increase in diclofenac systemic exposure. It is prudent to start with the lowest dose of ARTISOL-M and to monitor closely for signs of toxicity.

• There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

• Steady state plasma lithium and digoxin levels may be increased and ketoconazole levels may be decreased.

• Pharmacodynamic studies with diclofenac have shown no potentiation of oral hypoglycaemic and anticoagulant drugs. However as interactions have been reported with other NSAIDs, caution and adequate monitoring are, nevertheless advised.

• Because of decreased platelet aggregation caution is advised when using ARTISOL-M with anti-coagulants. NSAIDs may enhance the effects of anti-coagulants, such as warfarin, antiplatelet agents, such as acetylsalicylic acid, and serotonin re-uptake inhibitors (SSRIs) thereby increasing the risk of gastrointestinal bleeding.

• When diclofenac was administered with acetylsalicylic acid, the protein binding of diclofenac was reduced, although the clearance of the free diclofenac was not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac/misoprostol and acetylsalicylic acid is not generally recommended because of the potential risk of increased gastrointestinal adverse effects.

• Cases of hypo and hyperglycemia have been reported when diclofenac was associated with antidiabetic agents.

• Caution is advised when methotrexate is administered concurrently with NSAIDs because of possible enhancement of its toxicity by the NSAID as a result of increase in methotrexate plasma levels especially in patients receiving high doses of methotrexate.

• Concomitant use with other NSAIDs or with corticosteroids may increase the frequency of gastrointestinal ulceration or bleeding and of side effects generally.

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• Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists (AIIA) and beta-blockers: NSAIDs can reduce the efficacy of diuretics and other antihypertensive drugs, including ACE inhibitors, AIIA and beta-blockers.

• In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible. The occurrence of these interactions should be considered in patients taking diclofenac/misoprostol with an ACE inhibitor or an AIIA and/or diuretics.

• Antacids may delay the absorption of diclofenac. Magnesium-containing antacids have been shown to exacerbate misoprostol-associated diarrhea.

• Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

• NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

• Caution is recommended when co-prescribing diclofenac with mild CYP2C9 inhibitors (such as sulfapyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism. Caution is also recommended when co-prescribing diclofenac with moderate CYP2C9 inhibitors (such as fluconazole, miconazole and amiodarone). Concomitant administration of diclofenac with these moderate CYP2C9 inhibitors has not been studied, but is expected to lead to a larger magnitude of interaction.

OVERDOSE

Symptoms

Clinical signs that may indicate diclofenac overdose include gastrointestinal complaints, confusion, drowsiness, headache, dizziness, disorientation, excitation, coma, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible. Clinical signs that may indicate misoprostol overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia.

Management

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. Induced diuresis may be beneficial because diclofenac and misoprostol metabolites are excreted in the urine, provided that the patient does not develop renal failure at diclofenac overdose. Special measures such as

hemodialysis or haemoperfusion are probably unlikely to be helpful in accelerating the elimination of diclofenac and misoprostol, due to the high protein binding and extensive metabolism.

CONTRAINDICATIONS

ARTISOL-M is contraindicated in:

- Patients with active peptic ulcer/hemorrhage or perforation or who have active GI bleeding or other active bleedings e.g. cerebrovascular bleedings.
- Pregnant women and in women planning a pregnancy.
- Women of childbearing potential who are not using effective contraception.
- Patients with a known hypersensitivity to diclofenac, acetylsalicylic acid, other NSAIDs, misoprostol, other prostaglandins, or any other ingredient of the product.
- Patients in whom, attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory agents.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Patients with severe renal and hepatic failure.
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

STORAGE & INSTRUCTIONS:

Store between 15-25°C.

Protect from heat, sunlight and moisture.

Keep away from the reach of children.

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

HOW SUPPLIED

Artisol-M Tablet 50mg/200mcg

20 Tablets

Artisol-M Tablet 75mg/200mcg

20 Tablets

خوراک و طریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:

**PHARMASOL
PRIVATE LIMITED**

Plot # 549, Sundar Industrial Estate,
Lahore, Pakistan.