Mefenamic Acid

Dolfenal®

500 mg FILM-COATED TABLET

Non-Steroidal Anti-Inflammatory Drug

FORMULATION
Each film-coated tablet contains:
Mefenamic Acid…… 500 mg

PRODUCT DESCRIPTION
Mefenamic acid (Dolfenal®) 500 mg Tablet: Pink, elliptical film-coated tablet, scored on one side and plain on the other side

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Mefenamic acid exhibits anti-inflammatory, analgesic and antipyretic activities. It inhibits cyclooxygenase (COX)-1 and COX-2 isoenzymes, thus inhibiting prostaglandin synthesis in body tissues. Prostaglandins sensitize pain receptors to mechanical stimulation and to other chemical mediators (e.g., bradykinin, histamine).

Unlike other nonsteroidal anti-inflammatory drugs (NSAIDs), mefenamic acid appears to compete with prostaglandins for binding at the prostaglandin receptor site and thus potentially affect prostaglandins that have already been formed.

The anti-inflammatory, analgesic and antipyretic effects of mefenamic acid appear to result from inhibition of prostaglandin synthesis. These effects appear to be mediated principally through inhibition of COX-2 isoenzymes at inflammation sites.

PHARMACOKINETICS
Mefenamic acid is rapidly absorbed after oral administration. Peak plasma concentrations of approximately 10 to 20 mcg/mL are reached in 2 to 4 hours.

Mefenamic acid is extensively bound to plasma proteins (> 90%). The volume of distribution is 1.06 L/kg, following a 500 mg oral dose. It is not known if the drug or its metabolites cross the placenta. The drug is distributed into milk in very small amounts.

Mefenamic acid has a plasma half-life of two hours. Mefenamic acid is metabolized extensively in the liver by cytochrome P-450 (CYP) isoenzyme 2C9 to 3'-hydroxymethyl mefenamic acid; further oxidation to 3'-carboxyl-mefenamic acid may occur. Glucuronic acid conjugates of the drug and its metabolites are also formed.

About 52% of a dose of mefenamic acid is excreted in urine as glucuronic acid conjugates of the drug and its metabolites. About 20% of a dose is excreted in feces. Mefenamic acid is apparently not dialyzable.

Special Populations:

Hepatic Insufficiency: Hepatic metabolism is the significant pathway of mefenamic acid elimination; patients with acute and chronic hepatic disease may require reduced doses of mefenamic acid compared to patients with normal hepatic function.

Renal Insufficiency: Since mefenamic acid, its metabolites and conjugates are primarily excreted by the kidneys, the potential exists for mefenamic acid metabolites to accumulate. Mefenamic acid should not be given to patients with preexisting renal disease or in patients with significantly impaired renal function.

Poor CYP2C9 Metabolizers: In patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history or experience with other CYP2C9 substrates, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

INDICATIONS
- For the relief of mild to moderate pain including headache, dental pain, post-operative and postpartum pain, primary dysmenorrhea, and menorrhagia
- For the relief of musculoskeletal and joint disorders including osteoarthritis and rheumatoid arthritis

DOSAGE AND MODE OF ADMINISTRATION
Like other NSAIDs, the lowest effective dose should be used for the shortest possible time. After observing the response to initial therapy with this product, the dose and frequency should be adjusted to suit individual patient needs.

This medicine is given orally and may be taken with food or milk if stomach upset occurs.

Usual Recommended Dose in Adults and Adolescents older than 14 years:
1 tablet every 8 hours, as needed, or, as directed by a physician

For the relief of dysmenorrhea and premenstrual syndrome (PMS):
1 tablet every 8 hours while symptoms persist ("period pains" and other associated symptoms) or as directed by a physician.

- For relief of primary dysmenorrhea, mefenamic acid should be initiated with the onset of bleeding and associated symptoms, and should not be taken for more than 2 to 3 days.
- In menorrhagia, mefenamic acid should be given on the first day of excessive bleeding and continued as directed by a physician

For relief of acute pain, mefenamic acid should not be given for more than 7 days.

CONTRAINDICATIONS
- Known hypersensitivity to mefenamic acid, aspirin or NSAIDS, or to other ingredients in the product
- Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid reactions to NSAIDs have been reported in such patients.
- Patients with a history of gastrointestinal (GI) bleeding or perforation related to previous NSAID therapy
- Patients with previous or active ulceration or chronic inflammation of either the upper or lower GI tract
- Patients with a history of diarrhea with previous mefenamic acid therapy. Diarrhea may recur if mefenamic acid is taken again.
- Patients with severe cardiac, hepatic or renal disease
- Cerebrovascular bleeding or other bleeding disorders
- Known hyperkalemia
- Dengue fever, since NSAIDs may increase the risk of bleeding
- Third trimester of pregnancy, because of the risk of premature closure of the fetal ductus arteriosus and delay labor and birth
- Breastfeeding women, because of the potential for serious adverse reactions in breastfed infants
- Children and adolescents younger than 14 years old
- **Treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery**

WARNINGS AND PRECAUTIONS

Cardiovascular Risk
- Mefenamic acid may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- Exercise caution in patients with ischemic heart disease (e.g., myocardial infarction and/or angina), cerebrovascular disease (e.g., stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).
- The use of NSAIDs such as mefenamic acid can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure.

Gastrointestinal Risk
- NSAIDs, including mefenamic acid, cause an increased risk of serious GI 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 GI events.

General
Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Mefenamic acid is NOT recommended for use with other NSAIDs, with the exception of low-dose aspirin for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions (see ***Interactions with Other Medicaments***).

Cardiovascular Effects (see *Boxed Warnings*)
Cardiovascular Thrombotic Events: Clinical trials using COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. Patients with known cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should be alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed on the signs and/or symptoms of serious cardiovascular events and the steps to take if they occur.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial hemorrhage and bleeding diathesis.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events.

Hypertension: NSAIDs, including mefenamic acid, can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including mefenamic acid, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during 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. Mefenamic acid should be used with caution in patients with fluid retention or heart failure.

Endocrine/Metabolic Effects
Mefenamic acid is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids (see ***Interactions with Other Medicaments***).

Gastrointestinal Effects (see *Boxed Warnings*)
NSAIDs, including mefenamic acid, can cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small or large intestines, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.

NSAIDs should be prescribed with extreme caution in those with a history of ulcer disease or GI bleeding since these patients have a greater than 10-fold increased risk for developing a GI bleed compared with patients with neither of these risk factors. Other factors that increase the risk for 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. Elderly patients, in particular, are at greater risk for serious GI events.

The lowest effective dose should be used for the shortest possible duration to minimize the potential risk for an adverse GI event. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. Alternate therapies that do not involve NSAIDs should be considered especially for high-risk patients.

NSAIDs should be given with care in patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

Diarrhea occasionally occurs following the use of mefenamic acid. Although this may occur soon after starting treatment, it may also occur after several months of continuous use.

Genitourinary 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 an NSAID 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 Angiotensin Converting Enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Caution should be exercised when initiating treatment with mefenamic acid in patients with considerable dehydration.

Advanced Renal Disease: There are no controlled studies on the use of mefenamic acid in patients with advanced renal disease. Therefore, treatment with mefenamic acid is not recommended in these patients.

Anaphylactoid Reactions (see *Contraindications*)
Anaphylactoid reactions may occur in patients without known prior exposure to NSAIDs. Mefenamic acid 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. Mefenamic acid should be administered with caution to patients with preexisting asthma and emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions
Mefenamic acid 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 the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including mefenamic acid. These laboratory abnormalities may progress, may remain unchanged or may be transient with continuing therapy. Notable elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure, some with fatal outcomes have been reported.

Patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with NSAIDs. Discontinue mefenamic acid if clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash).

Hematologic Effects
Anemia is sometimes seen in patients receiving NSAIDs including mefenamic acid. Patients on long-term treatment with NSAIDs, including mefenamic acid, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. Mefenamic acid does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages.

Nervous System Effects
Headache: Prolonged use of any type of analgesic for headaches can make them worse. Medication-overuse headache should not be treated by increasing the dose. In such cases, the use of analgesics should be discontinued and the physician should be consulted.

Aseptic Meningitis: In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders, there may be an increased risk of aseptic meningitis.

Epilepsy: Caution should be exercised when treating patients suffering from epilepsy.

Prolonged Use
Patients on prolonged therapy should be kept under regular surveillance with particular attention to liver dysfunction, rash, blood dyscrasias or development of diarrhea.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If afflicted, patients should not drive or operate machinery.

CONCOMITANT DRUG	EFFECTS
ACE Inhibitors *(e.g., captopril, fosinopril, imidapril, enalapril)* ***and Angiotensin-II Receptor Antagonists*** *(e.g., losartan, telmisartan)*	• NSAIDs antagonize the hypotensive effect of ACE inhibitors and angiotensin-II receptor antagonists, and increase the risk of renal impairment.
Aminoglycosides *(e.g., gentamicin)*	• NSAIDs may reduce the excretion of aminoglycosides (increased risk of toxicity).
Antacids	• In a limited number of individuals, concomitant administration of an antacid containing 1.7 g of magnesium hydroxide with mefenamic acid 500 mg increased the Cmax of mefenamic acid by 125% and AUC by 36%.
Anticoagulants *(e.g., warfarin)*	• Increased risk of GI ulceration or bleeding; concurrent administration of NSAIDs and warfarin requires careful prothrombin time monitoring.
Antiplatelet Agents *(e.g., aspirin, clopidogrel, cilostazol)*	• Increased risk of GI ulceration or bleeding.
Aspirin, other NSAIDs *(e.g, ibuprofen, ketorolac, meloxicam)* ***including COX-2 Selective Inhibitors*** *(e.g., celecoxib, etoricoxib)*	• Avoid concomitant use of two or more NSAIDs, including aspirin and COX-2 selective inhibitors, because of the potential for increased adverse effects.
Cardiac glycosides *(e.g., digoxin)*	• NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma cardiac glycoside levels.
Ciclosporin, Tacrolimus	• Increased risk of nephrotoxicity when used with NSAIDs.
Corticosteroids	• Increased risk of GI ulceration or bleeding.
Diuretics *(e.g., thiazides, furosemide)*	• NSAIDs may reduce the natriuretic effects of thiazide diuretics and furosemide. Patients should be monitored for signs of renal failure and for efficacy of diuretic.
Drugs Affecting Hepatic Microsomal Enzymes	• Mefenamic acid is metabolized by CYP2C9, and concomitant use with drugs that inhibit this enzyme may result in altered safety and efficacy of mefenamic acid
Lithium	• Mefenamic acid may reduce the renal excretion of lithium (increased risk of toxicity).
Methotrexate	• NSAIDs may reduce the excretion of methotrexate (increased risk of toxicity).
Mifepristone	• NSAIDs should not be taken for 8 to 12 days after mifepristone administration since NSAIDs can reduce the effects of mifepristone.
Oral Hypoglycemic Agents *(e.g., sulfonylureas such as gliclazide, glipizide, glimepiride)*	• NSAIDs may inhibit the metabolism and prolong the half-life of sulfonylureas (increased risk of hypoglycemia).
Probenecid	• Reduced metabolism and elimination of NSAIDs and metabolites.
Protein-Bound Drugs *(e.g., hydantoins, sulfonamides, and sulfonylureas)*	• Mefenamic acid is highly protein bound and can be displaced from binding sites or it can displace other protein-bound drugs from binding sites. Patients on concomitant therapy should be observed for adverse effects.
Quinolone Antibiotics	• Increased risk of convulsions.
Selective Serotonin Reuptake Inhibitors (SSRIs) *(e.g., fluoxetine, citalopram, sertraline)*	• Increased risk of GI bleeding.
Zidovudine	• Increased risk of hematological toxicity.

Tell your doctor if you are taking other medicines, including vitamins, supplements, and herbal medicines.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy
Pregnancy Category C. Mefenamic acid is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong labor and birth. It is not known if mefenamic acid or its metabolites crosses the placenta. Caution should be exercised in prescribing mefenamic acid during the first and second trimesters of pregnancy (see ***Contraindications***).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

The use of mefenamic acid may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of mefenamic acid should be considered.

Lactation
Trace amounts of mefenamic acid may be present in breast milk. Because of the potential for serious adverse reactions from mefenamic acid in breastfeeding infants, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Children (< 14 years old)
The safety and efficacy in pediatric patients below 14 years old have not been established.

Elderly (≥ 65 years old)
Elderly and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs; the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

UNDESIRABLE EFFECTS

The most frequently reported undesirable effects (1 to 10%) of mefenamic acid include abdominal pain, abnormal kidney function, anemia, constipation, diarrhea, dizziness, dyspepsia, edema, elevated liver enzymes (e.g., alanine transaminase or aspartate transaminase), flatulence, GI ulcers (gastric/duodenal), gross bleeding/perforation, headache, heartburn, increased bleeding time, nausea, pruritus, rashes, tinnitus, and vomiting.

Less common adverse effects (<1% of patients) include:

Blood and Lymphatic System: Agranulocytosis, aplastic anemia, bone marrow hypoplasia, decreased hematocrit, disseminated intravascular coagulation, ecchymosis, eosinophilia, hemolytic anemia, leukopenia with a risk of infection, leukopenia, lymphadenopathy, neutropenia, pancytopenia, purpura, sepsis, thrombocytopenia

Immune System: Hypersensitivity reactions including anaphylaxis, respiratory tract reactivity (e.g., asthma, aggravated asthma, bronchospasm, or dyspnea), or skin reactions (e.g., pruritus, urticaria, purpura, angioedema, exfoliative or bullous dermatoses, SJS, TEN, erythema multiforme)

Metabolism and Nutrition: Appetite changes, fluid retention, glucose intolerance in diabetic patients, hyperglycemia, hyponatremia, weight changes

Psychiatric: Confusion, depression, nervousness

Nervous System: Anxiety, aseptic meningitis, asthenia, coma, convulsions, dream abnormalities, drowsiness, insomnia, meningitis, optic neuritis, paresthesia, reversible leukoencephalopathy, somnolence, tremors, vertigo

Eye Disorders: Blurred vision, conjunctivitis, eye irritation/pain, reversible loss of color vision, visual disturbances

Ear and Labyrinth: Ear pain, hearing impairment

Cardiovascular: Arrhythmia, congestive heart failure, hypertension, hypotension, myocardial infarction, palpitations, stroke, syncope, tachycardia, vasculitis

Respiratory, Thoracic and Mediastinal: Asthma, dyspnea, respiratory depression, pneumonia

Gastrointestinal: Anorexia, colitis, dry mouth, dyspepsia, enterocolitis, eructation, esophagitis, exacerbation of colitis and Crohn's disease, gastritis, glossitis, hematemesis, melena, pancreatitis, pyrosis, rectal bleeding, steatorrhea, ulcerative stomatitis

Hepatobiliary: Cholestatic jaundice, hepatic failure, hepatitis, hepatorenal syndrome, hepatotoxicity

Skin and Subcutaneous Tissue: Alopecia, exfoliative dermatitis, face edema, laryngeal edema, perspiration, photosensitivity, urticaria

Renal and Urinary: Acute interstitial nephritis, cystitis, dysuria, glomerulonephritis, hematuria, nephrotic syndrome, non-oliguric renal failure (particularly in dehydration), oliguria/polyuria, proteinuria, renal failure including renal papillary necrosis, tubulointerstitial nephritis

General Disorders: Death, fatigue, fever, infection, malaise, multi-organ failure

Investigations: False-positive for bile in the urine

OVERDOSE AND TREATMENT

Symptoms following acute overdose of NSAIDs, such as mefenamic acid, are usually limited to lethargy (fatigue), drowsiness, nausea, vomiting, and epigastric pain. GI bleeding can occur. Hypertension, acute kidney failure, respiratory depression, and coma may also occur. Anaphylactoid reactions have been reported with recommended doses of NSAIDs, and may occur following an overdose.

In humans who reportedly ingested 1.5 to 50 g of mefenamic acid, those with plasma drug concentrations ranging from 11 to 211 mcg/mL experienced tonic-clonic seizures, muscle twitching, vomiting, and diarrhea. Several other cases of seizures following ingestion of 5 to 50 g of mefenamic acid have also been reported.

Patients should be managed by symptomatic and supportive care after an NSAID overdose. There are no specific antidotes. In the event of overdose, emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or an osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Since mefenamic acid is highly bound to plasma proteins, forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS

Keep the product out of sight and reach of children.
Store at temperatures not exceeding 30°C.

AVAILABILITY

Mefenamic Acid (Dolfenal®) 500 mg film-coated tablets in flex foil, box of 100s.

DR-XY3915

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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