MEFENAMIC ACID CAPSULES BP 250 mg

MEFRIL-250

COMPOSITION:
Each Capsule contains
Mefenamic acid BP…. 250 mg

CHEMISTRY: Mefenamic acid is designated chemically as N-2, 3-xylylanthranilic acid

PHARMACOLOGY:
Mechanism of Action: Mefenamic acid is a non-steroidal anti-inflammatory agent with analgesic properties, and a demonstrable antipyretic effect. It has been shown to inhibit prostaglandin activity.

Pharmacokinetics:
Absorption: Mefenamic acid is absorbed from the gastrointestinal tract. Peak levels of 10mg/l occur two to four hours, with a half-life of 2 hours, after the administration of a 1g oral dose to adults.
Distribution: Mefenamic acid is extensively bound to plasma proteins.
Metabolism: Mefenamic acid metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered mefenamic acid with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.
Elimination: Following a single oral dose, 52% to 67% of the dose was recovered from the urine as unchanged drug or one of two metabolites. Assay of stools over 3 days accounted for 20% to 25% of the dose, chiefly as unconjugated metabolite II.

INDICATIONS AND USES:
Mefenamic acid capsules is used to relieve various types of pain such as: headache; body aches, rheumatoid arthritis, osteoarthritis; muscle and joint pains; toothache; sprains; painful menstruation (dysmenorrhea and menorrhagia); trauma-related pains.

CONTRAINDICATIONS:
- Hypersensitivity to the active substance or any of the excipients
- Inflammatory bowel disease.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure, hepatic failure and renal failure.
- History of hypersensitivity reaction to other NSAIDs.
- During the last trimester of pregnancy.
- Treatment of pain after coronary artery bypass graft (CABG) surgery.

SIDE EFFECTS / ADVERSE REACTIONS:
Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia, autoimmune hemolytic anemia*, bone marrow hypoplasia, decreased hematocrit, eosinophilia, leukopenia, pancytopenia, thrombocytopenic purpura, platelet aggregation inhibition.
Immune system disorders: Anaphylaxis.
Metabolism and nutrition disorders: Glucose intolerance in diabetic patients, hyponatremia, fluid retention.
Psychiatric disorders: Nervousness.
Nervous system disorders: Aseptic meningitis, blurred vision, convulsions, dizziness, drowsiness, headache, and insomnia.
Eye disorders: Eye irritation, reversible loss of color vision.
Ear and labyrinth disorders: Ear pain.
Cardiac disorders: Palpitation.
Vascular disorders: Hypotension, hypertension.
Respiratory, thoracic and mediastinal disorders: Asthma, dyspnea.
Gastrointestinal disorders: Gastrointestinal inflammation, gastrointestinal hemorrhage, gastrointestinal ulcer, gastrointestinal perforation.
The most frequently reported side effects associated with mefenamic acid involve the gastrointestinal tract. Diarrhea appears to be the most common side effect and is usually dose-related. It generally subsides on dosage reduction, and rapidly disappears on termination of therapy. Some patients may not be able to continue therapy.
The following are the most common gastrointestinal side effects: Abdominal pain, diarrhea and nausea with or without vomiting. *Less frequently reported gastrointestinal/Hepatobiliary side effects include:* Anorexia, cholestatic jaundice, colitis, constipation, and enterocolitis, and flatulence, gastric ulceration with and without hemorrhage, mild hepatic toxicity, hepatitis, hepatorenal syndrome, pyrosis, pancreatitis and steatorrhea.
Skin and subcutaneous tissue disorders: Angioedema, edema of the larynx, erythema multiforme, facial edema, Lyell's syndrome (toxic epidermal necrolysis), perspiration, pruritus, rash, Stevens-Johnson syndrome, urticaria and dermatitis exfoliative.
Renal and urinary disorders: Dysuria, hematuria, renal failure including papillary necrosis, and tubulointerstitial nephritis, glomerulonephritis, nephrotic syndrome.
General disorders and administration site conditions: Edema.
Investigations: Urobilinogen urine (false-positive), liver function test abnormal.
Pediatric patients: *General disorders and administration site conditions:* Hypothermia.
*Reports are associated with ≥12 months of mefenamic acid therapy and the anemia is reversible with discontinuation of therapy. Mefenamic capsule: Stop taking mefenamic acid immediately if the following potential side effects occur: loose bowel movement; nausea with or without vomiting; dizziness; eye irritation; excessive perspiration; skin rash or skin itching; drug reaction with eosinophilia and DRESS syndrome; upset stomach; drowsiness; insomnia; ear pain; mild liver toxicity; difficulty in breathing; cardiovascular events.

PRECAUTIONS AND WARNING:

The use of mefenamic acid with concomitant systemic non-aspirin NSAIDs including cyclooxygenase-2 (COX-2) inhibitors should be avoided. Concomitant use of a systemic NSAID and another systemic NSAID may increase frequency of gastrointestinal ulcers and bleeding.

Cardiovascular Effects: NSAIDs may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke which can be fatal. This risk may increase with duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with known CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimize the potential risk for an adverse CV event in patients treated with mefenamic acid, the lowest effective 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 toxicity and the steps to take if they occur (see Contraindications).

Hypertension: As with all NSAIDS, mefenamic acid can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. NSAIDs, including mefenamic acid, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with mefenamic acid and throughout the course of therapy.

Fluid Retention and Edema: As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking NSAIDs, including mefenamic acid. Therefore, mefenamic acid be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Gastrointestinal (GI) Effects: If diarrhea occurs, the dosage should be reduced or temporarily suspended. Symptoms may recur in certain patients following subsequent exposure.

NSAIDs including mefenamic acid 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 mefenamic acid, the treatment should be withdrawn. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with CV disease, patients using concomitant aspirin, corticosteroids, selective serotonin reuptake inhibitors, patients ingesting alcohol or patients with a prior history of, or active gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions. Therefore, mefenamic acid should be used with caution in these patients (see Contraindications).

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 mefenamic acid. 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. Mefenamic acid should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Laboratory Tests: A false-positive reaction for urinary bile, using the diazo tablet test, may result following mefenamic acid administration. If biliuria is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed.

Renal Effects: In rare cases, NSAIDs, including mefenamic acid, may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. NSAIDs inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of an NSAID may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome, overt renal disease and the elderly. Such patients should be carefully monitored while receiving NSAID therapy.

Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state. Since mefenamic acid metabolites are eliminated primarily by the kidneys, the drug should not be administered to patients with significantly impaired renal function.

Hematologic Effects: Mefenamic acid can inhibit platelet aggregation and may prolong prothrombin time in patients on warfarin therapy (see Interactions).

Hepatic Effects: Borderline elevations of one or more liver function tests may occur in some patients receiving mefenamic acid therapy. These elevations may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient 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 mefenamic acid. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, mefenamic acid should be discontinued.

Use with Oral Anticoagulants: The concomitant use of NSAIDs, including mefenamic acid, with oral anticoagulants increases the risk of GI and non-GI bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant (see Interactions).

Mefenamic acid capsule: Mefenamic Acid should not be taken continuously beyond seven days except on the advice of the doctor. Taking NSAIDs for very long periods of time or in very high doses increases the risk of stomach irritation, bleeding, as well as other side effects and should be done only under medical supervision.

Effects on Ability to Drive and Use Machines:

The effect of mefenamic acid on the ability to drive or use machinery has not been systematically evaluated.

DRUG INTERACTIONS:

Acetylsalicylic acid: Mefenamic acid interferes with the anti-platelet effect of low-dose aspirin, and thus may interfere with aspirin's prophylactic treatment of CV disease.

Anticoagulants: Mefenamic acid has been shown to displace warfarin from protein binding sites, and may enhance the response to oral anticoagulants. Therefore, concurrent administration of mefenamic acid with oral anticoagulant drugs requires frequent prothrombin time monitoring.

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 mefenamic acid with an ACE inhibitor or an AIIA and/or diuretics.

Therefore, the concomitant administration of these drugs should be done with caution, especially in elderly patients. Patients should be adequately hydrated and the need to monitor the renal function should be assessed in the beginning of the concomitant treatment and periodically thereafter.
Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.
Cyclosporine: Because of their effect on renal prostaglandins, NSAIDs such as mefenamic acid may increase the risk of nephrotoxicity with cyclosporine.
Hypoglycemic agents: There have been reports of changes in the effects of oral hypoglycemic agents in the presence of NSAIDs. Therefore, mefenamic acid should be administered with caution in patients receiving insulin or oral hypoglycemic agents.
Lithium: Mefenamic acid has produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when mefenamic acid and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.
Methotrexate: Caution is advised when methotrexate is administered concurrently with NSAIDs, including mefenamic acid, because NSAID administration may result in increased plasma levels of methotrexate, especially in patients receiving high doses of methotrexate.
Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Mefenamic Acid capsule:
Mefenamic Acid may interact with the following medications: Antiplatelet or Acetylsalicylic acid (e.g. Aspirin); Other nonsteroidal anti-inflammatory drugs; Corticosteroids; Anti-coagulants; Diuretics or other anti-hypertensives; Hypoglycemic agents; Methotrexate; Lithium; Tacrolimus; Cyclosporine.
If the patient is taking or about to take any of the previously mentioned medications, consult the doctor first before using mefenamic acid.

USE IN PREGNANCY AND LACTATION:
Pregnancy: Since there are no adequate and well-controlled studies in pregnant women, this drug should be used only if the potential benefits to the mother justify the possible risks to the fetus. It is not known if mefenamic acid or its metabolites cross the placenta. However, because of the effects of drugs in this class (i.e., inhibitors of prostaglandin synthesis) on the fetal CV system (e.g., premature closure of the ductus arteriosus), the use of mefenamic acid in pregnant women is contraindicated during the third trimester of pregnancy.
Mefenamic acid inhibits prostaglandin synthesis which may result in prolongation of pregnancy and interference with labor when administered late in the pregnancy. Women on mefenamic acid therapy should consult their physician if they decide to become pregnant.
Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.
If used during second or third trimester of pregnancy, NSAIDs may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible. Pregnant women on mefenamic acid should be closely monitored for amniotic fluid volume.
Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.
Lactation: Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. Therefore, mefenamic acid should not be taken by nursing mothers.
Fertility: Based on the mechanism of action, the use of NSAIDs may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including mefenamic acid should be considered.

DOSAGE AND ADMINISTRATION:
Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms.
The oral dosage form of mefenamic acid may be taken with food if gastrointestinal upset occurs.
Mild to moderate pain/rheumatoid arthritis/osteoarthritis in adults and adolescents over 14 years of age: 500 mg three times daily.
Dysmenorrhea: 500 mg three times daily, to be administered at the onset of menstrual pain and continued while symptoms persist according to the judgment of the physician.
Menorrhagia: 500 mg three times daily, starting with the onset of bleeding and associated symptoms and continued according to the judgment of the physician.

OVERDOSAGE, SYMPTOMS AND ANTIDOTE:
Following accidental overdosage, the stomach should be emptied immediately by inducing emesis or by gastric lavage, followed by administration of activated charcoal. Vital functions should be monitored and supported. Hemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins.
Seizures, acute renal failure, coma, confusional state, vertigo, and hallucination have been reported with mefenamic acid overdoses. Overdose has led to fatalities.

STORAGE:
Store below 30°C. Keep in a cool, dry place.

DATE OF PUBLICATION:
November 2022

SIN10125P

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