**Mefenamic Acid Capsules USP**

**DESCRIPTION**
Mefenamic acid is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each ivory capsule contains 250 mg of mefenamic acid for oral administration. Mefenamic acid is a white to greyish-white, odorless, microcrystalline powder with a melting point of 230° to 231°C and water solubility of 0.004% at pH 7.1. The chemical name is N-2,3-xylylanthranilic acid. The molecular weight is 241.29. Its molecular formula is C_{17}H_{16}NO_2 and the structural formula of mefenamic acid is:

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\[
\begin{align*}
\text{COOH} & \\
\text{NH} & \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]
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Each capsule also contains lactose monohydrate and magnesium stearate. The capsule shell contains gelatin, sodium lauryl sulfate, titanium dioxide, D&C yellow No. 10, FD&C yellow No. 6 and FD&C red No. 3.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**
Mefenamic acid has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of mefenamic acid, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

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

**Pharmacokinetics**

**Absorption**
Mefenamic acid is rapidly absorbed after oral administration. In two 500-mg single oral dose studies, the mean extent of absorption was 30.5 mcg/hr/mL (17%CV). The bioavailability of the capsule relative to an IV dose or an oral solution has not been studied.

Following a single 1-gram oral dose, mean peak plasma levels ranging from 10 to 20 mcg/ml have been reported. Peak plasma levels are attained in 2 to 4 hours and the elimination half-life approximates 2 hours. Following multiple doses, plasma levels are proportional to dose with no evidence of drug accumulation. In a multiple dose trial of normal adult subjects (n=6) receiving 1-gram doses of mefenamic acid four times daily, steady-state concentrations of 20 mcg/mL were reached on the second day of administration, consistent with the short half-life.

The effect of food on the rate and extent of absorption of mefenamic acid has not been studied. Concomitant ingestion of antacids containing magnesium hydroxide has been shown to significantly decrease the rate and extent of mefenamic acid absorption (see PRECAUTIONS: Drug Interactions).

**Distribution**
Mefenamic acid has been reported as being greater than 90% bound to albumin. The relationship of unbound fraction to drug concentration has not been studied. The apparent volume of distribution (V_{ss}F) estimated following a 500-mg oral dose of mefenamic acid was 1.06 L/kg.

Based on its physical and chemical properties, mefenamic acid is expected to be excreted in human breast milk (see PRECAUTIONS: Nursing Mothers).

**Elimination**

**Metabolism**
Mefenamic acid is metabolized by cytochrome P450 enzyme CYP2C9 to 3-hydroxyethyl mefenamic acid (Metabolite I). Further oxidation to a 3-carboxyethylmefenamic acid (Metabolite II) may occur. The activity of these metabolites has not been studied. The metabolites may undergo glucuronidation and mefenamic acid is also glucuronidated directly. A peak plasma level approximating 20 mcg/mL was observed at 3 hours for the hydroxy metabolite and its glucuronide (n=6) after a single 1-gram dose. Similarly, a peak plasma level of 8 mcg/mL was observed at 6 to 8 hours for the carboxy metabolite and its glucuronide.

**Excretion**
Approximately fifty-two percent of a mefenamic acid dose is excreted into the urine primarily as glucuronides of mefenamic acid (6%), 3-hydroxymefenamic acid (25%) and 3-carboxyethylmefenamic acid (21%). The fecal route of elimination accounts for up to 20% of the dose, mainly in the form of unconjugated 3-carboxyethylmefenamic acid.

**Elimination half-life of mefenamic acid is approximately two hours. Half-lives of metabolites I and**
**Gastrointestinal Bleeding, Ulceration, and Perforation**

They occur. Patients should be informed about the symptoms of serious CV events and the steps to take if necessary. To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the early signs of such events.

The increase in CV thrombotic risk has been observed most consistently at higher doses. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at the highest effective doses. To minimize the potential risk for adverse CV events in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as mefenamic acid, increases the risk of serious gastrointestinal (GI) events (see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation).

**TABLE 1. Pharmacokinetic Parameter Estimates for Mefenamic Acid**

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Normal Healthy Adults (18 to 45 yr)</th>
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</thead>
<tbody>
<tr>
<td>Value</td>
<td>CV</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2</td>
</tr>
<tr>
<td>Oral clearance (L/hr)</td>
<td>21.13</td>
</tr>
<tr>
<td>Apparent volume of distribution; Vz/F (L/kg)</td>
<td>1.08</td>
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<tr>
<td>Half-life; t½ (hrs)</td>
<td>2 to 4</td>
</tr>
</tbody>
</table>

**Special Populations**

**Pediatric:**

Mefenamic acid has not been adequately investigated in pediatric patients less than 14 years of age. A study in 17 preterm infants administered 2 mg/kg indicated that the half-life was about five times as long as adults, consistent with the slow metabolism of mefenamic acid in newborn infants. The mean Tmax in this study was 4 mcg/mL (range 2.9 to 6.1). The mean time to maximum concentration (Tmax) was 8 hours (range 2 to 18 hours).

**Race:**

Pharmacokinetic differences due to race have not been identified.

**Hepatic Impairment:**

Mefenamic acid is a hepatic drug and hepatic metabolism is a significant pathway of mefenamic acid elimination, with patients with acute and chronic hepatic disease may require reduced doses of mefenamic acid compared to patients with normal hepatic function (see WARNINGS; Hepatotoxicity).

**Renal Impairment:**

Mefenamic acid is eliminated primarily by the kidney. The increase in CV thrombotic risk has been observed most consistently at higher doses. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at the highest effective doses. To minimize the potential risk for adverse CV events in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as mefenamic acid, increases the risk of serious gastrointestinal (GI) events (see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation).

**Drug Interaction Studies**

**Aspirin:**

When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin (see PRECAUTIONS; Drug Interactions).

**Clinical Studies**

In controlled, double-blind, clinical trials, mefenamic acid was evaluated for the treatment of primary dysmenorrhea. The parameters used in determining efficacy included pain assessment by both patient and investigator; the need for concurrent analgesic medication; and evaluation of change in frequency and severity of symptoms characteristic of dysmenorrhea. Patients received either mefenamic acid, 500 mg (2 capsules) as an initial dose of 250 mg every 6 hours, or placebo at onset of bleeding or of pain, whichever began first. After three menstrual cycles, patients were crossed over to the alternate treatment for an additional three cycles. Mefenamic acid was significantly superior to placebo in all parameters, and both treatments (drug and placebo) were equally tolerated.

**INDICATIONS AND USAGE**

Carefully consider the potential benefits and risks of mefenamic acid capsules and other treatment options before deciding to use mefenamic acid capsules. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation). Mefenamic acid capsules are indicated:

- For relief of mild to moderate pain in patients ≥14 years of age, when therapy will not exceed one week (7 days).
- For treatment of primary dysmenorrhea.

**CONTRAINDICATIONS**

Mefenamic acid capsules are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reaction and serious skin reactions) to mefenamic acid or any components of the drug product (see WARNINGS; Anaphylactic Reactions, Serious Skin Reactions).
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.

Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients (see WARNINGS; Anaphylactic Reaction, Exacerbation of Asthma Related to Aspirin Sensitivity).
- In the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS; Cardiovascular Thrombotic Events).

**WARNINGS**

**Cardiovascular Thrombotic Events**

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, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate.

Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses. To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as mefenamic acid, increases the risk of serious gastrointestinal (GI) events (see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation).
Statin Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG (see CONTRAINDICATIONS).

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person-years in NSAID-treated patients compared to 12 per 100 person-years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of mefenamic acid in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If mefenamic acid is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including mefenamic acid, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptom, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is asymptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy, concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking, use of alcohol, older age, and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue mefenamic acid until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding (see PRECAUTIONS; Drug Interactions).

Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including mefenamic acid.

Inform patients of the warning signs and symptom of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue mefenamic acid immediately, and perform a clinical evaluation of the patient.

Hypertension

NSAIDs, including mefenamic acid, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazides diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs (see PRECAUTIONS; Drug Interactions). Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists’ Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalization for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of mefenamic acid may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) (see PRECAUTIONS; Drug Interactions).

Avoid the use of mefenamic acid in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If mefenamic acid is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity and Hyperkalemia

Renal Toxicity

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 prostaglandin 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, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of mefenamic acid in patients with advanced renal disease. The renal effects of mefenamic acid may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating mefenamic acid. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of mefenamic acid (see PRECAUTIONS; Drug Interactions). Avoid the use of mefenamic acid in patients with advanced renal disease unless the benefits are expected to outweigh the risk of
Inform patients that the concomitant use of mefenamic acid with other NSAIDs or salicylates (e.g., aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of gastrointestinal bleeding, ulceration, and perforation). Mefenamic acid cannot be expected to substitute for corticosteroids or to treat 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.

Information for Patients
Advertise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families and their caregivers of the following information before initiating therapy with mefenamic acid and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events
Advertise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately (see WARNINGS; Cardiovascular Thrombotic Events).

Gastrointestinal Bleeding, Ulceration, and Perforation
Advertise patients to report symptoms of ulceration and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their healthcare provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding (see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation).

Hepatotoxicity
Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop mefenamic acid and seek immediate medical therapy (see WARNINGS; Hepatotoxicity).

Heart Failure and Edema
Advertise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur (see WARNINGS; Heart Failure and Edema).

Anaphylactic Reactions
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur (see CONTRAINDICATIONS, WARNINGS; Anaphylactic Reactions).

Serious Skin Reactions
Advertise patients to stop mefenamic acid immediately if they develop any type of rash and contact their healthcare provider as soon as possible (see WARNINGS; Serious Skin Reactions).

Female Fertility
Advertise females of reproductive potential who desire pregnancy that NSAIDs, including mefenamic acid, may be associated with a reversible delay in ovulation (see PRECAUTIONS; Carcinogenesis, Mutagenesis, Impairment of Fertility).

Fetal Toxicity
Inform pregnant women to avoid use of mefenamic acid and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closure of the fetal ductus arteriosus (see WARNINGS; Premature Closure of Fetal Ductus Arteriosus).

Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of mefenamic acid with other NSAIDs or salicylates (e.g.,
Pregnancy

In another study, rats administered up to 10-times a human dose of 250 mg showed decreased fertility.

Recommended Human Dose [MRHD] of 1500 mg/day on a mg/m² basis for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with mefenamic acid until they talk to their healthcare provider (see PRECAUTIONS; Drug Interactions).

Masking of Inflammation and Fever

The pharmacological activity of mefenamic acid in reducing inflammation, and possibly fever may diminish the utility of diagnostic signs in detecting infections.

Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile checked periodically (see WARNINGS; Gastrointestinal Bleeding, Ulceration and Perforation, and Hepatotoxicity).

Drug Interactions

See Table 2 for clinically significant drug interactions with mefenamic acid.

### Table 2: Clinically Significant Drug Interactions with Mefenamic Acid

<table>
<thead>
<tr>
<th>Drugs That Interfere with Hemostasis</th>
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<tbody>
<tr>
<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
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<tr>
<td><strong>Aspirin</strong></td>
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<tr>
<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
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<tr>
<td><strong>ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers</strong></td>
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<tr>
<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
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<tr>
<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
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<tr>
<td><strong>Digoxin</strong></td>
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<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
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<tr>
<td><strong>Lithium</strong></td>
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<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
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<tr>
<td><strong>Methotrexate</strong></td>
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<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
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<tr>
<td><strong>Cyclosporine</strong></td>
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<tr>
<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
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<tr>
<td><strong>NSAIDs and Salicylates</strong></td>
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<td><strong>Clinical Impact:</strong></td>
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<tr>
<td><strong>Intervention:</strong></td>
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<td><strong>Pemetrexed</strong></td>
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<td><strong>Clinical Impact:</strong></td>
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<td><strong>Intervention:</strong></td>
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<td><strong>Antacid</strong></td>
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<tr>
<td><strong>Clinical Impact:</strong></td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
</tr>
</tbody>
</table>

**Drug/Laboratory Test Interactions**

Mefenamic acid may prolong prothrombin time. Therefore, when the drug is administered to patients receiving oral anticoagulant drugs, frequent monitoring of prothrombin time is necessary. A false-positive reaction for urinary bile, using the dios tablet test, may result after mefenamic acid administration. If bilirubia is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenesis:

Long-term studies in animals to evaluate the carcinogenic potential of mefenamic acid have not been conducted.

Mutagenesis:

Studies to evaluate the mutagenic potential of mefenamic acid have not been completed.

**Impairment of Fertility:**

Dietary administration of mefenamic acid to male rats 61 days- and to female rats 15 days- prior to mating through Gestation Day (GD) 21 at a dose of 155 mg/kg/day (equivalent to the Maximum Recommended Human Dose [MRHD] of 1500 mg/day on a mg/m² basis) resulted in decreased corpora lutea.

In another study, rats administered up to 10-times a human dose of 250 mg showed decreased fertility.

**Pregnancy**
Fever, infection, sepsis

Additional adverse experiences reported occasionally and listed here by body system include: pruritus, rashes, tinnitus

In patients taking mefenamic acid or other NSAIDs, the most frequently reported adverse experiences may not reflect the rates observed in practice. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience

The following adverse reactions are discussed in greater detail in other sections of the labeling: Cardiovascular Thrombotic Events, Gastrointestinal Bleeding, Ulceration, and Perforation, Hematopoietic, Renal Toxicity and Hyperkalemia, Precautions; Laboratory Monitoring.

Clinical studies of mefenamic acid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As with any NSAID, caution should be exercised in treating the elderly (65 years and older). This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Treated dams were associated with decreased weight gain and delayed parturition. In another study, dietary administration of mefenamic acid at a dose 1.2-times the MRHD from gestation day (GD) 15 to weaning resulted in an increased incidence of perinatal death.

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, decreased pup survival occurred and increased the incidence of stillbirth. The effects of mefenamic acid on labor and delivery in pregnant women are unknown.

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including mefenamic acid, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including mefenamic acid, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 14 have not been established.

Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects (see WARNINGS; Cardiovascular Thrombotic Events, Gastrointestinal Bleeding, Ulceration, and Perforation, Hematopoietic, Renal Toxicity and Hyperkalemia, PRECAUTIONS; Laboratory Monitoring).

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Cardiovascular system
Congestive heart failure, hypertension, tachycardia, syncope

Digestive system
Dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice

Hemic and lymphatic system
Ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia

Metabolic and nutritional
Weight changes

Nervous system
Amnesia, asthenia, confusion, depression, drowsiness; insomnia; malaise; nervousness; paresthesia; somnolence; tremors; vertigo

Respiratory system
Asthma, dyspnea

Skin and appendages
Alopecia, photosensitivity, pruritus, sweat

Special senses
Blurred vision

OVERDOSAGE
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression and coma have occurred, but were rare (see WARNINGS; Cardiovascular Thrombotic Events, Gastrointestinal Bleeding, Ulceration, and Perforation, Hypertension, Renal Toxicity and Hyperkalemia).

Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdose (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdosage treatment, contact a poison control center (1-800-222-1222).

DOSAGE AND ADMINISTRATION
Carefully consider the potential benefits and risks of mefenamic acid and other treatment options before deciding to use mefenamic acid. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation). After observing the response to initial therapy with mefenamic acid, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of acute pain in adults and adolescents ≥14 years of age, the recommended dose is 500 mg as an initial dose followed by 250 mg every 6 hours as needed, usually not to exceed one week.

For the treatment of primary dysmenorrhea, the recommended dose is 500 mg as an initial dose followed by 250 mg every 6 hours, given orally, starting with the onset of menses and should not be necessary for more than 2 to 3 days.

HOW SUPPLIED
Mefenamic acid capsules USP, 250 mg are available as size ‘1’ capsules having ivory cap and ivory body imprinted with “LU” on cap and “R31” on body in black ink, containing white to off white granular powder.

They are supplied as follows:
NDC 68180-185-06 Bottles of 30's
NDC 68180-185-01 Bottles of 100's
NDC 68180-185-13 24 (3 x 8) unit dose capsules
Dispense in a tight container as defined in the USP.

Storage:
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States
Manufactured by:
Lupin Limited
Goa 403 722
INDIA
Revised: June 11, 2016
ID#: 247373

MEDICATION GUIDE
Mefenamic (me-fe-NAM-ik) Acid Capsules USP
Rx only

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAID can cause serious side effects, including:
- Increase risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)": Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- Increase risk of bleeding, ulcers and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:
- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problem.

NSAID should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- or the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:
- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell our healthcare provider about all of your medical conditions, including if you:
- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 29 weeks of pregnancy
- are breastfeeding or plan to breastfeed

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins, or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first.

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?"

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problem including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- Other side effects if NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID and call your healthcare provider right away if you get any of the following symptoms:
nausea
more tired or weaker than usual
diarrhea
itching
your skin or eyes look yellow
indigestion or stomach pain
flu-like symptoms
vomit blood
there is blood in the bowel movement or it is black and sticky like tar
unusual weight gain
skin rash or blisters with fever
swelling of the arms, legs, hands, and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all of the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or Lupin Pharmaceuticals, Inc at 1-800-399-2561.

Other information about NSAIDs
Aspirin is an NSAID medicine but it does not increase the chance of a heart attack.
Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAID for more than 10 days.

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Manufactured by:
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Goa 403 722
INDIA.

Revised: June 11, 2016
ID#: 247374

PACKAGE LABEL:PRINCIPAL DISPLAY PANEL
MEFENAMIC ACID CAPSULES USP
Rx ONLY
250 mg
NDC No.: 68180-185-01
10s Pack

MEFENAMIC ACID
mefenamic acid capsule

Product Information

Product Type
HUMAN PRESCRIPTION DRUG

Item Code (Source)
NDC:68180-185

Route of Administration
ORAL

Active Ingredient/Active Moiety
Ingredient Name
Basis of Strength
Strength
MEFENAMIC ACID (UNII: 367589PJ2C) (MEFENAMIC ACID - UNII:367589PJ2C) MEFENAMIC ACID 250 mg

Inactive Ingredients

Ingredient Name
Strength
DAC YELLOW NO. 18 (UNII: Z6GZ5G560I)
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)
FD&C YELLOW NO. 5 (UNII: 8FT78RAR6)
FERROSOFERRIC OXIDE (UNII: XM0M87F357)
GELATIN (UNII: 2G86QN327L)
FERROSOFERRIC OXIDE (UNII: XM0M87F357)
GELATIN (UNII: 2G86QN327L)
GELATIN (UNII: 2G86QN327L)
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FERROSOFERRIC OXIDE (UNII: XM0M87F357)
MAGNESIUM STEARATE (UNII: 5YX9G79GD5)
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)
PROPYLENE GLYCOL (UNII: EDC09207V3)
SHELLAC (UNII: 46N107B71O)
Lupin Pharmaceuticals, Inc.

**Product Characteristics**

- **Color:** YELLOW (Ivory Cap and Ivory Body)
- **Shape:** CAPSULE
- **Size:** 19mm
- **Flavor:** Imprint Code: LU;R31

**Packaging**

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**Marketing Information**

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**Labeler** - Lupin Pharmaceuticals, Inc. (089153071)

**Registrant** - LUPIN LIMITED (675521013)

**Establishment**

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