

MEFENAMIC ACID- mefenamic acid capsule
Misemer Pharmaceuticals, Inc

Mefenamic Acid

BOXED WARNING

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (See WARNINGS).
- Mefenamic acid is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (See WARNINGS).

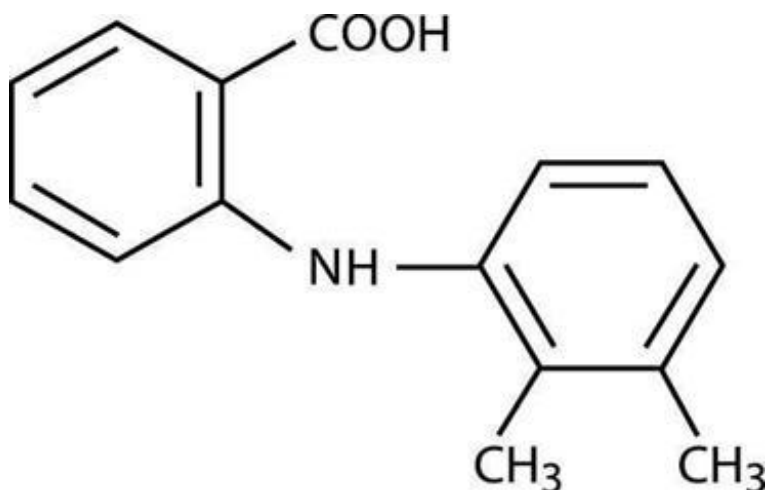
Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal 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 gastrointestinal events (See WARNINGS).

DESCRIPTION

Mefenamic acid is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each green-banded, yellow 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°-231°C and water solubility of 0.004% at pH 7.1. The chemical name is N-2,3-xylanthranilic acid. The molecular weight is 241.29. Its molecular formula is C₁₅H₁₅NO₂ and the structural formula of mefenamic acid is:



Each capsule also contains lactose monohydrate. The capsule shell and band contain dimethicone, D&C yellow No. 10, FD&C blue No. 1 aluminum lake, FD&C yellow No. 6, gelatin, propylene glycol, shellac, titanium dioxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of mefenamic acid, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

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).^{1,2} 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 10-20 mcg/mL³ 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 increase the rate and extent of mefenamic acid absorption (see PRECAUTIONS, Drug Interactions).¹

Distribution

Mefenamic acid has been reported as being greater than 90% bound to albumin.⁹ The relationship of unbound fraction to drug concentration has not been studied. The apparent volume of distribution (V_{ZSS}/F) estimated following a 500-mg oral dose of mefenamic acid was 1.06 L/kg.²

Based on its physical and chemical properties, mefenamic acid is expected to be excreted in human breast milk.

Metabolism

Mefenamic acid is metabolized by cytochrome P450 enzyme CYP2C9 to 3-hydroxymethyl mefenamic acid (Metabolite I). Further oxidation to a 3-carboxymefenamic acid (Metabolite II) may occur.¹⁰ 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 6-8 hours for the carboxy metabolite and its glucuronide.³

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-carboxymefenamic acid (21%). The fecal route of elimination accounts for up to 20% of the dose, mainly in the form of unconjugated 3-carboxymefenamic acid.³

The elimination half-life of mefenamic acid is approximately two hours. Half-lives of metabolites I and II have not been precisely reported, but appear to be longer than the parent compound.³ The metabolites may accumulate in patients with renal or hepatic failure. The mefenamic acid glucuronide may bind irreversibly to plasma proteins. Because both renal and hepatic excretion are significant pathways of elimination, dosage adjustments in patients with renal or hepatic dysfunction may be necessary. Mefenamic acid should not be administered to patients with preexisting renal disease or in patients with significantly impaired renal function.

TABLE 1. Pharmacokinetic Parameter Estimates for Mefenamic Acid

PK Parameters	Normal Healthy Adults (18-45 yr)	
	Value	CV
T _{max} (hr)	2	66
Oral clearance (L/hr)	21.23	38
Apparent volume of distribution; V _z /F (L/kg)	1.06	60
Half-life; t _{1/2} (hrs)	2 to 4	NA

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 low activity of metabolic enzymes in newborn infants. The mean C_{max} in this study was 4 mcg/mL (range 2.9-6.1). The mean time to maximum concentration (T_{max}) was 8 hours (range 2-18 hrs).¹¹

Race

Pharmacokinetic differences due to race have not been identified.

Hepatic Insufficiency

Mefenamic acid pharmacokinetics have not been studied in patients with hepatic dysfunction. As hepatic metabolism is a 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

Mefenamic acid pharmacokinetics have not been investigated in subjects with renal insufficiency. Given that 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 administered to patients with pre-existing

renal disease or in patients with significantly impaired renal function.

CLINICAL STUDIES

In controlled, double-blind, clinical trials, mefenamic acid was evaluated for the treatment of primary spasmodic 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 spasmodic 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 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).

Mefenamic acid is 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 is contraindicated in patients with known hypersensitivity to mefenamic acid.

Mefenamic acid should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

Mefenamic acid is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Mefenamic acid is contraindicated in patients with acute active ulceration or chronic inflammation of either the upper or lower gastrointestinal tract.

Mefenamic acid should not be used in patients with pre-existing renal disease.

WARNINGS

CARDIOVASCULAR EFFECTS

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, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, 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 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 does increase the risk of serious GI events (see GI WARNINGS).

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

Hypertension

NSAIDs, including mefenamic acid, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV 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 (BP) should be monitored closely during the 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.

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation

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. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at sometime during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to 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 anti-coagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians 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. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs have 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 a nonsteroidal anti-inflammatory drug 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 ACE-inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available for controlled studies regarding the use of mefenamic acid in patients with advanced renal disease. Therefore, treatment with mefenamic acid is not recommended in these patients with advanced renal disease (see CONTRAINDICATIONS).

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to mefenamic acid. 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 (see CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including 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.

Pregnancy

In late pregnancy, as with other NSAIDs, mefenamic acid should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

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.

The pharmacological activity of mefenamic acid in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

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 ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported.

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 clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), mefenamic acid should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including mefenamic acid. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. 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. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving mefenamic acid who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, mefenamic acid should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Information for Patients

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that

accompanies each prescription dispensed.

1. Mefenamic acid, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Cardiovascular Effects).
2. Mefenamic acid, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalizations and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulceration and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation).
3. Mefenamic acid, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see WARNINGS).
7. In late pregnancy, as with other NSAIDs, mefenamic acid should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, mefenamic acid should be discontinued.

Drug Interactions

A number of compounds are inhibitors of CYP2C9. Drug interactions studies of mefenamic acid and these compounds have not been conducted. The possibility of altered safety and efficacy should be considered when mefenamic acid is used concomitantly with these drugs.

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin

When mefenamic acid is administered with aspirin, its protein binding is reduced, although the clearance of free mefenamic acid is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of MEFENAMIC ACID and aspirin is not generally recommended because of the potential of increased adverse effects.

Diuretics

Clinical studies, as well as post marketing observations, have shown that mefenamic acid can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy of NSAIDs, the patient should be observed closely for signs of renal failure (see PRECAUTIONS, Renal Effects), as well as to assure diuretic efficacy.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Antacids

In a single dose study (n=6), ingestion of an antacid containing 1.7-gram of magnesium hydroxide with 500-mg of mefenamic acid increased the C_{max} and AUC of mefenamic acid by 125% and 36%, respectively. ¹

Drug/Laboratory Test Interactions

Mefenamic acid may prolong prothrombin time. ⁴ 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 diazo tablet test, may result after

mefenamic acid administration. If biliuria is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed.

Pregnancy

Teratogenic Effects:

Pregnancy Category C.

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate or well controlled studies in pregnant women. Mefenamic acid should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

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

Nursing Mothers

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant.⁷ Because of the potential for serious adverse reactions in nursing infants from mefenamic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

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 NSAIDs, 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 (see CLINICAL PHARMACOLOGY and ADVERSE EVENTS).

ADVERSE REACTIONS

In patients taking mefenamic acid or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1-10% of patients are:

Gastrointestinal experiences including - abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal), vomiting, abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, tinnitus.

Additional adverse experiences reported occasionally and listed here by body system include:

Body as a whole - fever, infection, sepsis

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 - anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness; insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo

Respiratory system - asthma, dyspnea

Skin and appendages - alopecia, photosensitivity, pruritus, sweat

Special senses - blurred vision

Urogenital system - cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions, which occur rarely are:

Body as a whole - anaphylactoid reactions, appetite changes, death

Cardiovascular system - arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive system - eructation, liver failure, pancreatitis

Hemic and lymphatic system - agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia

Metabolic and nutritional - hyperglycemia

Nervous system - convulsions, coma, hallucinations, meningitis

Respiratory - respiratory depression, pneumonia

Skin and appendages - angioedema, toxic epidermal necrosis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special senses - conjunctivitis, hearing impairment

OVERDOSAGE

Symptoms following acute NSAIDs overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or 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). Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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).

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. ⁴

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 bleeding and associated symptoms. Clinical studies indicate that effective treatment can be initiated with the start of menses and should not be necessary for more than 2 to 3 days. ⁵

HOW SUPPLIED

Mefenamic acid is available as 250 mg green-banded, yellow capsules, imprinted with "BP" on the cap and "629" on the body in green ink. Bottles of 30, NDC# 0276-0509-30.

Dispense in a tight container as defined in the USP.

Storage

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

Medication Guide

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 problems

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 have 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. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. You should not take NSAIDs after about 30 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 taking 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.

PRINCIPAL DISPLAY PANEL

The image shows the principal display panel for Mefenamic Acid Capsules, USP. The panel is white with purple and orange accents. At the top left is the Misemer logo. To its right is 'Rx Only'. Below the logo is the NDC number 'NDC 0276-0509-30'. The product name 'Mefenamic Acid Capsules, USP' is prominently displayed in blue and black. Below this is a warning box: 'ATTENTION PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY TO EACH PATIENT'. At the bottom left, there are fields for 'GTIN', 'LOT', 'EXP', and 'S/N'. In the center bottom, an orange pill-shaped graphic contains '250 mg', and a purple pill-shaped graphic contains '30 CAPSULES'. On the right side, there is detailed text: 'Description: Each capsule contains: Mefenamic Acid, USP 250 mg'; 'Usual Dosage: See package insert for full prescribing information. Adults and adolescents over 14 years of age: 500 mg as an initial dose, followed by 250 mg at six-hour intervals.'; 'Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure. Please see important safety information. KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.'; 'Storage: Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].'; 'Distributed by: Misemer Pharmaceutical, Inc, Ripley, MS 38663'; 'Manufactured by: Lotus Pharmaceutical Co., Ltd, Nantou Plant No. 30, Chenggong 1st Road, Sinsing Village, Nantou City, Nantou County, 54066, Taiwan'; and '050930 Rev: 08/21'. At the bottom right, there is a barcode with the number '3 02760 50930 5' and 'L677L-01-SKP R-2108' below it.

MISEMER Rx Only

NDC 0276-0509-30

Mefenamic Acid
Capsules, USP

**ATTENTION PHARMACIST: PLEASE DISPENSE WITH
MEDICATION GUIDE PROVIDED SEPARATELY TO
EACH PATIENT**

GTIN LOT EXP S/N

250 mg

30 CAPSULES

Description: Each capsule contains:
Mefenamic Acid, USP 250 mg

Usual Dosage: See package insert for full prescribing information.
Adults and adolescents over 14 years of age: 500 mg as an initial dose,
followed by 250 mg at six-hour intervals.

Pharmacist: Dispense in a tight, light-resistant container as defined in
the USP, with a child-resistant closure.
Please see important safety information.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Storage: Store at 20°-25°C (68°-77°F); excursions permitted to
15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Distributed by:
Misemer Pharmaceutical, Inc
Ripley, MS 38663

Manufactured by:
Lotus Pharmaceutical Co., Ltd.
Nantou Plant No. 30
Chenggong 1st Road,
Sinsing Village,
Nantou City, Nantou County,
54066, Taiwan

050930
Rev: 08/21

L677L-01-SKP R-2108

3 02760 50930 5

MEFENAMIC ACID

mefenamic acid capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0276-0509
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
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
GELATIN (UNII: 2G86QN327L)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
DIMETHICONE (UNII: 92RU3N3Y1O)	

Product Characteristics

Color	yellow	Score	no score
Shape	CAPSULE	Size	17mm
Flavor		Imprint Code	BP;629
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0276-0509-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/01/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091608	11/01/2021	

Labeler - Misemer Pharmaceuticals, Inc (784121365)

Establishment

Name	Address	ID/FEI	Business Operations
Lotus Pharmaceutical Co., Ltd		658828103	manufacture(0276-0509)

Revised: 12/2022

Misemer Pharmaceuticals, Inc