

PONSTEL - mefenamic acid capsule

Shionogi Inc.

PONSTEL®

(Mefenamic Acid Capsules, USP)

250 mg

Rx only

Cardiovascular Risk

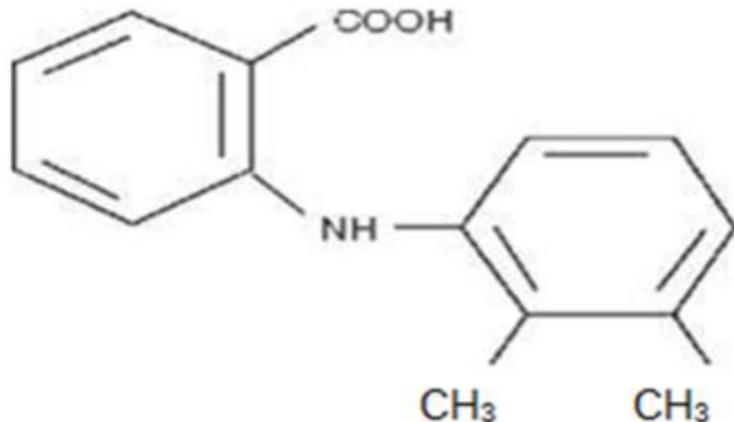
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (See **WARNINGS**).
- PONSTEL® 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

PONSTEL® (mefenamic acid) is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each blue-banded, 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°-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 C₁₅H₁₅N₂O₂ and the structural formula of mefenamic acid is:



Each capsule also contains lactose, NF. The capsule shell and/or band contains citric acid, USP; D&C yellow No. 10; FD&C blue No. 1; FD&C red No. 3; FD&C yellow No. 6; gelatin, NF; glycerol monooleate; silicon dioxide, NF; sodium benzoate, NF; sodium lauryl sulfate, NF; titanium dioxide, USP.

CLINICAL PHARMACOLOGY

Pharmacodynamics

PONSTEL is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of PONSTEL, 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 1020 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 ($V_{z,ss}/F$) estimated following a 500-mg oral dose of mefenamic acid was 1.06 L/kg.²

Based on its physical and chemical properties, PONSTEL 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. PONSTEL 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)	21.13	38
Apparent volume of distribution; V _z /F (L/kg)	1.06	60
Half-life; t _{1/2} (hrs)	2 to 4	N/A

Special Populations

Pediatric: PONSTEL 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 hours).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 PONSTEL 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. PONSTEL should not be administered to patients with preexisting renal disease or in patients with significantly impaired renal function.

Clinical Studies

In controlled, double-blind, clinical trials, PONSTEL 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 PONSTEL, 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. PONSTEL 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 PONSTEL and other treatment options before deciding to use PONSTEL. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

PONSTEL is indicated:

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

CONTRAINDICATIONS

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

PONSTEL 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**).

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

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

PONSTEL should not be used in patients with preexisting 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 PONSTEL, can lead to onset of new hypertension or worsening of pre-existing 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 PONSTEL, 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. PONSTEL should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including PONSTEL, 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 PONSTEL in patients with advanced renal disease. Therefore, treatment with PONSTEL 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 PONSTEL. PONSTEL 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 PONSTEL, 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, PONSTEL should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

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

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including PONSTEL. 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 PONSTEL, 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 PONSTEL who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting 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, PONSTEL should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting 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. PONSTEL, 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. PONSTEL, 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. PONSTEL, 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, PONSTEL 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, PONSTEL 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 PONSTEL 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 PONSTEL is administered with aspirin, its protein binding is reduced, although the clearance of free PONSTEL 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 PONSTEL 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

PONSTEL 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. PONSTEL 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 PONSTEL on labor and delivery in pregnant women are unknown.

Nursing Mothers

Trace amounts of PONSTEL 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 PONSTEL, 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 PONSTEL 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 PONSTEL 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, lymph-adenopathy, 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 PONSTEL and other treatment options before deciding to use PONSTEL. 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 PONSTEL, 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

PONSTEL (mefenamic acid) is available as 250 mg blue-banded, ivory capsules, imprinted with “ FHPC 400” and “PONSTEL®”.

Bottles of 30 NDC 59630-400-30

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].

REFERENCES

1. Neuvonen PJ, Kivisto KT: Enhancement of drug absorption by antacids. An unrecognized drug interaction. Clin Pharmacokinet. 27:120-8, Aug 1994.
2. Tall AR, Mistilits SP: Studies on Ponstan (mefenamic acid): I. Gastro-intestinal blood loss; II. Absorption and excretion of a new formulation. J Int Med Res (UK). 1975, 3 (3) p176-82.
3. Winder CV, Kaump DH, Glazko et al: Experimental observations of flufenamic, mefenamic, and meclofenamic acids. AnnPhys Med (Eng), Suppl p7-49.1967.
4. Glazko AJ: Experimental observations of flufenamic, mefenamic, and meclofenamic acids. Part III. Metabolic disposition, in Fenamates in Medicine. A Symposium, London, 1966. Annals of Physical Medicine, Supplement, pp 23-36, 1967.
5. Data on file, First Horizon (Protocol 356).
6. Budoff PW: Use of mefenamic acid in the treatment of primary dysmenorrhea. JAMA. 241: 2713-2716, 1979.
7. Buchanan RA, et al. The breast milk excretion of mefenamic acid. Curr Ther Res. 10:592, 1968.
8. Corby DG, Decker WJ: Management of acute poisoning with activated charcoal. Pediatrics. 54:324,1974.
9. Champion GD, Graham GG: Pharmacokinetics of non-steroidal anti-inflammatory agents. Aust NZ J Med. 8 (Supp 1): 94-100, Jun 1978.
10. McGurk KA, Rimmel RP, Hosagrahara VP, Tosh D, Burchell B: Reactivity of mefenamic acid 1-o- acyl glucuronide with proteins in vitro and ex vivo. Drug Metab Dispos. Aug 1996, 24 (8) p842-9.
11. Ito K, Niida Y, Sato J et al: Pharmacokinetics of mefenamic acid in preterm infants with patent ductus arteriosus. Acta Paediatr JPN. 36 (4): 387-91, 1994.

Distributed by:

Shionogi Inc.

Florham Park, NJ 07932

MEDICATION GUIDE

for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.

This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment.

Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called “corticosteroids” and “anticoagulants”
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- or the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines 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 a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects.

Keep a list of all of your medicines to show to your healthcare provider and pharmacist.

- If you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- If you are breastfeeding. **Talk to you doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

<p>Serious side effects include:</p> <ul style="list-style-type: none">• heart attack• stroke• high blood pressure• heart failure from body swelling (fluid retention)• kidney problems including kidney failure• bleeding and ulcers in the stomach and intestine• low red blood cells (anemia)• life-threatening skin reactions• life-threatening allergic reactions• liver problems including liver failure• asthma attacks in people who have asthma	<p>Other side effects include:</p> <ul style="list-style-type: none">• stomach pain• constipation• diarrhea• gas• heartburn• nausea• vomiting• dizziness
---	--

Get emergency help right away if you have 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 medicine and call your healthcare provider right away if you have any of the following symptoms:

•nausea	•there is blood in your bowel movement or it is black and sticky like tar
•more tired or weaker than usual	•unusual weight gain
•itching	•stomach pain
•your skin or eyes look yellow	•skin rash or blisters with fever
•flu-like symptoms	•swelling of the arms and legs, hands and feet
•vomit blood	

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (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 of these NSAID medicines 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.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	PONSTEL
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naprosyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or call Shionogi Inc. at 1-800-849-9707.

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

PON-PI-8

Revised 05/12

Principal Display Panel

NDC 59630-400-30

Ponstel®
(Mefenamic Acid Capsules, USP)
250 mg
Rx only
30 Capsules
SHIONOGI INC.

NDC 59630-400-30

Exp. Date: _____
Lot No.: _____

UNVARNISHED

Please see important safety information.

Keep this and all drugs out of the reach of children.

Dosage and Use: See accompanying prescribing information.

PONSTEL®
(Mefenamic Acid Capsules, USP)
250 mg
Rx Only
30 CAPSULES
PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE
SHIONOGI INC.

Dispense in a tight container as defined in the USP.
Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). (See USP Controlled Room Temperature).
Rev. 04/12
PON-L30-4

Distributed by:
Shionogi Inc.
Florham Park, NJ 07932

3 59630 40030 9

Revised: 11/2012

Distributed by: Shionogi Inc.