CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

15-034 / S- 034

Trade Name: **Ponstel**

Generic Name: **mefenamic acid capsules**

Sponsor: **Parke Davis**

Approval Date: **October 4, 2001**

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15-034 / S- 034

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Medical Review(s)	**X**
Chemistry Review(s)	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	

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15-034 / S- 034

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 15-034/S-034

Parke-Davis
Attention: James A. Parker, Jr.
Director, Advertising and Labeling
Worldwide Regulatory Affairs
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Parker:

Please refer to your supplemental new drug application dated August 14, 1998, received August 17, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ponstel (mefenamic acid) Capsules, 250 mg.

We acknowledge receipt of your submission dated August 14, 1998.

This supplemental new drug application provides for additions to the package insert to add a Geriatric Use subsection in accordance with 21 CFR 201.57(f)(10).

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 14, 1998).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 15-034/S-034." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Acting Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonca Bull
10/4/01 10:34:52 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

15-034 / S- 034

LABELING

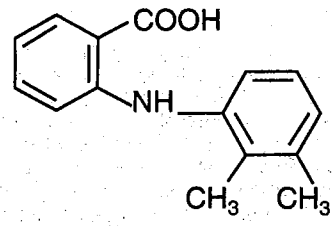
4-4

Ponstel
0540G152

Ponstel®
(Mefenamic Acid)

DESCRIPTION

Ponstel (mefenamic acid) is N-(2,3-xylyl)-anthranilic acid. It is an analgesic agent for oral administration. Ponstel is available in capsules containing 250 mg of mefenamic acid. 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. The structural formula of mefenamic acid is:



It is a white powder with a melting point of 230°–231°C, molecular weight 241.28, and water solubility of 0.004% at pH 7.1.

CLINICAL PHARMACOLOGY

Ponstel is a nonsteroidal agent with demon-

CLINICAL PHARMACOLOGY

Ponstel is a nonsteroidal agent with demonstrated antiinflammatory, analgesic, and antipyretic activity in laboratory animals.[1,2] The mode of action is not known. In animal studies, Ponstel was found to inhibit prostaglandin synthesis and to compete for binding at the prostaglandin receptor site.[3]

Pharmacologic studies show Ponstel did not relieve morphine abstinence signs in abstinent, morphine-habituated monkeys.[1]

Following a single 1-gram oral dose, peak plasma levels of 10 µg/mL occurred in 2 to 4 hours with a half-life of 2 hours. Following multiple doses, plasma levels are proportional to dose with no evidence of drug accumulation. One gram of Ponstel given four times daily produces peak blood levels of 20 µg/mL by the second day of administration.[4]

Following a single dose, sixty-seven percent of the total dose is excreted in the urine as unchanged drug or as one of two metabolites. Twenty to twenty-five percent of the dose is excreted in the feces during the first three days.[4]

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

Ponstel is indicated for the relief of moderate pain[5] when therapy will not exceed one week. Ponstel is also indicated for the treatment of primary dysmenorrhea.[5,6]

Studies in children under 14 years of age have been inadequate to evaluate the safety and effectiveness of Ponstel.

CONTRAINDICATIONS

Ponstel should not be used in patients who have previously exhibited hypersensitivity to it.

Because the potential exists for cross-sensitivity to aspirin or other nonsteroidal antiinflammatory drugs, Ponstel should not be given to patients in whom these drugs induce symptoms of bronchospasm, allergic rhinitis, or urticaria.

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

Ponstel should be avoided in patients with preexisting renal disease.

WARNINGS

If diarrhea occurs, the dosage should be reduced or temporarily suspended (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION). Certain patients who develop diarrhea may be unable to tolerate the drug because of recurrence of the symptoms on subsequent exposure.

Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc, no risk factors (eg, age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

If rash occurs, administration of the drug should be stopped.

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.

Renal Effects: As with other nonsteroidal antiinflammatory drugs, long-term administration of mefenamic acid to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and 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 the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Since Ponstel is eliminated primarily by the kidneys, the drug should not be administered to patients with significantly impaired renal functions.

As with other nonsteroidal antiinflammatory drugs, borderline elevations of one or more liver tests may occur in some patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. 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 more severe hepatic reaction while on therapy with Ponstel. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with other nonsteroidal antiinflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc), Ponstel should be discontinued.

Information for Patients: Patients should be advised that if rash, diarrhea, or other digestive problems arise, they should stop the drug and consult their physician.

Patients in whom aspirin or other nonsteroidal antiinflammatory drugs induce symptoms of bronchospasm, allergic rhinitis, or urticaria should be made aware that the potential exists for cross-sensitivity to Ponstel.

The long-term effects, if any, of intermittent Ponstel therapy for dysmenorrhea are not known. Women on such therapy should consult their physician if they should decide to become pregnant.

PARKE-DAVIS

Ponstel (Mefenamic Acid)

Ponstel, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (nonsteroidal antiinflammatory drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy).

Drug Interactions: Ponstel may prolong prothrombin time.[5] Therefore, when the drug is administered to patients receiving oral anticoagulant drugs, frequent monitoring of prothrombin time is necessary.

Use in Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rats, rabbits, and dogs. Rats given up to 10 times the human dose showed decreased fertility, delay in parturition, and a decreased rate of survival to weaning. Rabbits at 2.5 times the human dose showed an increase in the number of resorptions. There were no fetal anomalies observed in these studies nor in dogs at up to 10 times the human dose.[5]

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed.

The use of Ponstel in late pregnancy is not recommended because of the effects on the fetal cardiovascular system of drugs of this class.

Nursing Mothers: Trace amounts of Ponstel may be present in breast milk and transmitted to the nursing infant; thus, Ponstel should not be taken by the nursing mother because of the effects on the infant cardiovascular system of drugs of this class.

Use in Children: Safety and effectiveness in children below the age of 14 have not been established.

ADVERSE REACTIONS

Gastrointestinal: The most frequently reported adverse reactions associated with the use of Ponstel involve the gastrointestinal tract. In controlled studies for up to eight months, the following disturbances were reported in decreasing order of frequency: diarrhea (approximately 5% of patients), nausea with or without vomiting, other gastrointestinal symptoms, and abdominal pain.

In certain patients, the diarrhea was of sufficient severity to require discontinuation of medication. The occurrence of the diarrhea is usually dose related, generally subsides on reduction of dosage, and rapidly disappears on termination of therapy.

Other gastrointestinal reactions less frequently reported were anorexia, pyrosis, flatulence, and constipation.

Gastrointestinal ulceration with and without hemorrhage has been reported.

Hematopoietic: Cases of autoimmune hemolytic anemia have been associated with the continuous administration of Ponstel for 12 months or longer. In such cases the Coombs test results are positive with evidence of both accelerated RBC production and RBC destruction. The process is reversible upon termination of Ponstel administration.

Decreases in hematocrit have been noted in 2%-5% of patients and primarily in those who have received prolonged therapy. Leukopenia, eosinophilia, thrombocytopenic purpura, agranulocytosis, pancytopenia, and bone marrow hypoplasia have also been reported on occasion.

Nervous System: Drowsiness, dizziness, nervousness, headache, blurred vision, and insomnia have occurred.

Integumentary: Urticaria, rash, and facial edema have been reported.

Renal: As with other nonsteroidal antiinflammatory agents, renal failure, including papillary necrosis, has been reported. In elderly patients renal failure has occurred after taking Ponstel for 2-6 weeks. The renal damage may not be completely reversible. Hematuria and dysuria have also been reported with Ponstel.

Other: Eye irritation, ear pain, perspiration, mild hepatic toxicity, and increased need for insulin in a diabetic have been reported. There have been rare reports of palpitation, dyspnea, and reversible loss of color vision.

OVERDOSAGE

Although doses up to 6000 mg/day have been given, no specific information is available on the management of acute massive overdosage. Should accidental overdosage occur, the stomach should be emptied by inducing emesis or by careful gastric lavage followed by the administration of activated charcoal.[6] Laboratory studies indicate that Ponstel should be adsorbed from the gastrointestinal tract by activated charcoal.[4] Vital functions should be monitored and supported. Because mefenamic acid and its metabolites are firmly bound to plasma proteins, hemodialysis and peritoneal dialysis may be of little value.[4]

DOSAGE AND ADMINISTRATION

Administration is by the oral route, preferably with food.

The recommended regimen in acute pain for adults and children over 14 years of age is 500 mg as an initial dose followed by 250 mg every six hours as needed, usually not to exceed one week.[5]

For the treatment of primary dysmenorrhea, the recommended dosage is 500 mg as an initial dose followed by 250 mg every 6 hours, 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.[6]

HOW SUPPLIED

N 0071-0540-24 (P-D 540) Ponstel (mefenamic acid) is available as 250 mg capsules in bottles of 100.

REFERENCES

1. Winder CV, et al: Antiinflammatory, antipyretic and antinociceptive properties of N-(2,3-xylyl) anthranilic acid (mefenamic acid). *J Pharmacol Exp Ther* 138: 405-413, 1962.

2. Wax J, et al: Comparative activities, tolerances and safety of nonsteroidal antiinflammatory agents in rats. *J Pharmacol Exp Ther* 192: 172-178, 1975.

3. Ferreira SH, Vane JR: Aspirin and prostaglandins, in *The Prostaglandins,* Ramwell PW Ed, Plenum Press, NY, vol. 2, 1974, pp 1-47.

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, Medical Affairs Dept. Parke-Davis.

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.

Direct Medical Inquiries to: Parke-Davis
Div of Warner-Lambert Co, 201 Tabor Road
Morris Plains, NJ 07950
Att: Medical Affairs Department

Caution—Federal law prohibits dispensing without prescription.

0540G152

Revised May 1995

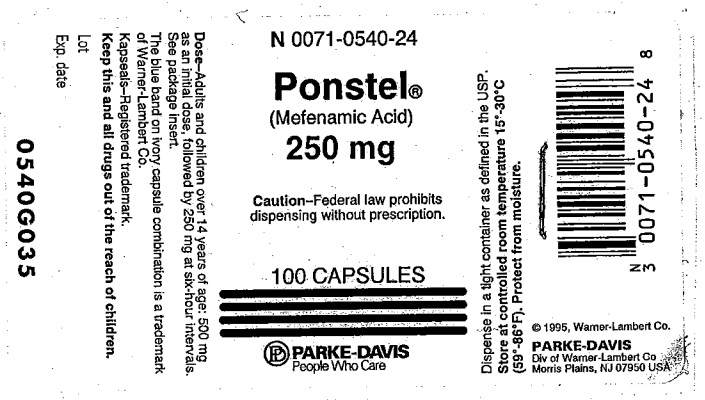
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

0540G152

Annual Report

Ponstel® 250 mg Kapseals®
(Mefenamic Acid Capsules, USP)

NDA 15-034



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

15-034 / S- 034

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Labeling and Clinical Review of Supplemental Labeling Revisions (SLRs):

Sponsor: Parke-Davis Pharmaceutical

Products: Ponstel® (mefenamic acid) Capsule, 250mg

Materials Reviewed:

NDA 15-034 (Capsule):

SLR	Date submitted	Date received	Date completed
034	August 14, 1998	August 17, 1998	September 13, 2001

Background:
On August 14, 1998, Parke-Davis Pharmaceuticals sent a letter to the agency stating that they had added the proper labeling for geriatric use as explained in 21 CFR 201.57(f)(10). The manufacture has complied with 21 CFR 201.57(f)(10), which describes the appropriate use of drugs in the elderly. The manufactured also complied with subsections CFR 201.57(f)(10)(ii)(A); CFR 201.57(f)(10)(iii)(B); CFR 201.57(f)(10)(iv). These subsections deal with what to state if there were not sufficient numbers of subjects aged 65 and older, if the drug is excreted substantially in the kidney and if the drug causes a specific hazard, respectively.

Conclusions/Recommendations:
These labeling changes are acceptable. An approval letter should be sent advising the applicant that these supplemental NDA submissions be approved.

Melanie Simmons Pharm D (C)
University of Iowa

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/s/

Mary Jane Walling
10/3/01 12:04:30 PM
CSO

Mary Jane Walling
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