CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-049/-015

Trade Name: Pentasa Controlled Release Tablets , 250 mg

Generic Name: meslamine

Sponsor: Shire Pharmaceutical Development, Inc.

Approval Date: July 8, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-049/S-015

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Labeling	X
Medical Review(s)	
Chemistry Review(s)	X
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-049/S-015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-049/S-015

Shire Pharmaceutical Development Inc.
Attention: Raj Kishore, Ph. D.
Senior Director, Regulatory Affairs
1801 Research Blvd., Suite 600
Rockville, MD 20850

Dear Kishore:

Please refer to your supplemental new drug application dated March 8, 2004, received March 8, 2004 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Pentasa® (meslamine) Controlled Release Capsules, 250 mg.

We acknowledge receipt of your submission dated July 6, 2004 containing requested blister package labeling.

This supplemental new drug application provides for the addition of a new strength (500 mg capsule).

We completed our review of this application, as amended. This application is approved on draft labeling, effective the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

Listed changes

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the 1) draft package insert submitted March 8, 2004 ((b)(4)----------, 2) draft sample package carton submitted March 8, 2004 identified (b)(4)---------- ----------, 3) draft carton label submitted March 8, 2004 identified (b)(4)------ ---- ----------, 4) draft container label submitted March 8, 2004 identified (b)(4)----------, (b)(4)-------, and 5) draft blister label submitted July 6, 2004 (b)(4)----------

1. Draft Package Insert ((b)(4)----------):
   a. The "prescribing information as of date" should be updated from June 1999.
   b. Change the "Rx" to read "Rx only" in the package insert.

2. Draft Sample Pack Carton identified(b)(4)---------- ----------:
   The "250 mg" on the side panel should be updated to read "500 mg".

3. The word "capsules" should follow the words "controlled-release" wherever the established name appears on all carton sizes.

These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-049/S-015". Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Betsy Scroggs, Pharm.D., Consumer Safety Office at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
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/

Robert Justice
7/8/04 01:33:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-049/S015

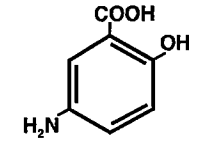
LABELING

PENTASA®
(mesalamine)

Controlled-Release Capsules 250 mg and 500 mg
Prescribing Information as of July 2004 **Rx only**

DESCRIPTION

PENTASA (mesalamine) for oral administration is a controlled-release formulation of mesalamine, an aminosalicylate anti-inflammatory agent for gastrointestinal use.
Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid. It has a molecular weight of 153.14.
The structural formula is:



Each 250 mg capsule contains 250 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains D&C Yellow #10, FD&C Blue #1, FD&C Green #3, gelatin, titanium dioxide, and other ingredients.
Each 500 mg capsule contains 500 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains FD&C Blue #1, gelatin, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Sulfasalazine is split by bacterial action in the colon into sulfapyridine (SP) and mesalamine (5-ASA). It is thought that the mesalamine component is therapeutically active in ulcerative colitis. The usual oral dose of sulfasalazine for active ulcerative colitis in adults is 2 to 4 g per day in divided doses. Four grams of sulfasalazine provide 1.6 g of free mesalamine to the colon.
The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, ie, prostanoids, and through the lipoxygenase pathways, ie, leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

Human Pharmacokinetics and Metabolism

Absorption. PENTASA is an ethylcellulose-coated, controlled-release formulation of mesalamine designed to release therapeutic quantities of mesalamine throughout the gastrointestinal tract. Based on urinary excretion data, 20% to 30% of the mesalamine in PENTASA is absorbed. In contrast, when mesalamine is administered orally as an unformulated 1-g aqueous suspension, mesalamine is approximately 80% absorbed.
Plasma mesalamine concentration peaked at approximately 1 μg/mL 3 hours following a 1-g PENTASA dose and declined in a biphasic manner. The literature describes a mean terminal half-life of 42 minutes for mesalamine following intravenous administration. Because of the continuous release and absorption of mesalamine from PENTASA throughout the gastrointestinal tract, the true elimination half-life cannot be determined after oral administration. N-acetylmesalamine, the major metabolite of mesalamine, peaked at approximately 3 hours at 1.8 μg/mL, and its concentration followed a biphasic decline. Pharmacological activities of N-acetylmesalamine are unknown, and other metabolites have not been identified.
Oral mesalamine pharmacokinetics were nonlinear when PENTASA capsules were dosed from 250 mg to 1 g four times daily, with steady-state mesalamine plasma concentrations increasing about nine times, from 0.14 μg/mL to 1.21 μg/mL, suggesting saturable first-pass metabolism. N-acetylmesalamine pharmacokinetics were linear.
Elimination. About 130 mg free mesalamine was recovered in the feces following a single 1-g PENTASA dose, which was comparable to the 140 mg of mesalamine recovered from the molar equivalent sulfasalazine tablet dose of 2.5 g. Elimination of free mesalamine and salicylates in feces increased proportionately with PENTASA dose. N-acetylmesalamine was the primary compound excreted in the urine (19% to 30%) following PENTASA dosing.

CLINICAL TRIALS

In two randomized, double-blind, placebo-controlled, dose-response trials (UC-1 and UC-2) of 625 patients with active mild to moderate ulcerative colitis, PENTASA, at an oral dose of 4 g/day given 1 g four times daily, produced consistent improvement in prospectively identified primary efficacy parameters, PGA, Tx F, and SI as shown in the table below.
The 4-g dose of PENTASA also gave consistent improvement in secondary efficacy parameters, namely the frequency of trips to the toilet, stool consistency, rectal bleeding, abdominal/rectal pain, and urgency. The 4-g dose of PENTASA induced remission as assessed by endoscopic and symptomatic endpoints. In some patients, the 2-g dose of PENTASA was observed to improve efficacy parameters measured. However, the 2-g dose gave inconsistent results in primary efficacy parameters across the two adequate and well-controlled trials.

	Clinical Trial UC-1			Clinical Trial UC-2		
		PENTASA			PENTASA	
Parameter Evaluated	PL (n=90)	4 g/day (n=95)	2 g/day (n=97)	PL (n=83)	4 g/day (n=85)	2 g/day (n=83)
PGA	36%	59%*	57%*	31%	55%*	41%
Tx F	22%	9%*	18%	31%	9%*	17%*
SI	−2.5	−5.0*	−4.3*	−1.6	−3.8*	−2.6
Remission†	12%	26%*	24%*	12%	27%*	12%

* $p < 0.05$ vs placebo.
PGA: Physician Global Assessment: proportion of patients with complete or marked improvement.
Tx F: Treatment Failure: proportion of patients developing severe or fulminant UC requiring steroid therapy or hospitalization or worsening of the disease at 7 days of therapy, or lack of significant improvement by 14 days of therapy.
SI: Sigmoidoscopic Index: an objective measure of disease activity rated by a standard (15-point) scale that includes mucosal vascular pattern, erythema, friability, granularity/ulcerations, and mucopus: improvement over baseline.
† Defined as complete resolution of symptoms plus improvement of endoscopic endpoints. To be considered in remission, patients had a "1" score for one of the endoscopic components (mucosal vascular pattern, erythema, granularity, or friability) and "0" for the others.

INDICATIONS AND USAGE

PENTASA is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

CONTRAINDICATIONS

PENTASA is contraindicated in patients who have demonstrated hypersensitivity to mesalamine, any other components of this medication, or salicylates.

PRECAUTIONS

General

Caution should be exercised if PENTASA is administered to patients with impaired hepatic function.
Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence cannot be ascertained, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close medical supervision at reduced dose and only if clearly needed.

Renal

Caution should be exercised if PENTASA is administered to patients with impaired renal function. Single reports of nephrotic syndrome and interstitial nephritis associated with mesalamine therapy have been described in the foreign literature. There have been rare reports of interstitial nephritis in patients receiving PENTASA. In animal studies, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis. Patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria should be carefully monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m^2/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.
No evidence of mutagenicity was observed in an in vitro Ames test and an in vivo mouse micronucleus test.
No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).
Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials.

Pregnancy
Category B. Reproduction studies have been performed in rats at doses up to 1000 mg/kg/day (5900 mg/M^2) and rabbits at doses of 800 mg/kg/day (6856 mg/M^2) and have revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PENTASA should be used during pregnancy only if clearly needed.
Mesalamine is known to cross the placental barrier.

Nursing Mothers
Minute quantities of mesalamine were distributed to breast milk and amniotic fluid of pregnant women following sulfasalazine therapy. When treated with sulfasalazine at a dose equivalent to 1.25 g/day of mesalamine, 0.02 µg/mL to 0.08 µg/mL and trace amounts of mesalamine were measured in amniotic fluid and breast milk, respectively. N-acetylmesalamine, in quantities of 0.07 µg/mL to 0.77 µg/mL and 1.13 µg/mL to 3.44 µg/mL, was identified in the same fluids, respectively.
Caution should be exercised when PENTASA is administered to a nursing woman.

Pediatric Use
Safety and efficacy of PENTASA in pediatric patients have not been established.

ADVERSE REACTIONS
In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received PENTASA therapy. Generally, PENTASA therapy was well tolerated. The most common events (ie, greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).
In two domestic placebo-controlled trials involving over 600 ulcerative colitis patients, adverse events were fewer in PENTASA-treated patients than in the placebo group (PENTASA 14% vs placebo 18%) and were not dose-related. Events occurring at 1% or more are shown in the table below. Of these, only nausea and vomiting were more frequent in the PENTASA group. Withdrawal from therapy due to adverse events was more common on placebo than PENTASA (7% vs 4%).

Table 1. Adverse Events Occurring in More Than 1% of Either Placebo or PENTASA Patients in Domestic Placebo-controlled Ulcerative Colitis Trials. (PENTASA Comparison to Placebo)

Event	PENTASA n=451	Placebo n=173
Diarrhea	16 (3.5%)	13 (7.5%)
Headache	10 (2.2%)	6 (3.5%)
Nausea	14 (3.1%)	---
Abdominal Pain	5 (1.1%)	7 (4.0%)
Melena (Bloody Diarrhea)	4 (0.9%)	6 (3.5%)
Rash	6 (1.3%)	2 (1.2%)
Anorexia	5 (1.1%)	2 (1.2%)
Fever	4 (0.9%)	2 (1.2%)
Rectal Urgency	1 (0.2%)	4 (2.3%)
Nausea and Vomiting	5 (1.1%)	---
Worsening of Ulcerative Colitis	2 (0.4%)	2 (1.2%)
Acne	1 (0.2%)	2 (1.2%)

Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematologic, liver, and kidney function.
The following adverse events, presented by body system, were reported infrequently (ie, less than 1%) during domestic ulcerative colitis and Crohn's disease trials. In many cases, the relationship to PENTASA has not been established.
Gastrointestinal: abdominal distention, anorexia, constipation, duodenal ulcer, dysphagia, eructation, esophageal ulcer, fecal incontinence, GGTP increase, GI bleeding, increased alkaline phosphatase, LDH increase, mouth ulcer, oral moniliases, pancreatitis, rectal bleeding, SGOT increase, SGPT increase, stool abnormalities (color or texture change), thirst
Dermatological: acne, alopecia, dry skin, eczema, erythema nodosum, nail disorder, photosensitivity, pruritus, sweating, urticaria
Nervous System: depression, dizziness, insomnia, somnolence, paresthesia
Cardiovascular: palpitations, pericarditis, vasodilation
Other: albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocythemia, thrombocytopenia, urinary frequency
One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by one physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.
Published case reports and/or spontaneous postmarketing surveillance have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, hepatitis, aplastic anemia, pancytopenia, leukopenia, agranulocytosis, or anemia while receiving mesalamine therapy. Anemia can be a part of the clinical presentation of inflammatory bowel disease. Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy.

Postmarketing Reports
The following events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:
Gastrointestinal: Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, billrubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome which included hepatic function changes was also reported.

OVERDOSAGE
Single oral doses of mesalamine up to 5 g/kg in pigs or a single intravenous dose of mesalamine at 920 mg/kg in rats were not lethal.
There is no clinical experience with PENTASA overdosage. PENTASA is an aminosalicylate, and symptoms of salicylate toxicity may be possible, such as: tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting, and diarrhea. Severe intoxication with salicylates can lead to disruption of electrolyte balance and blood pH, hyperthermia, and dehydration.
Treatment of Overdosage. Since PENTASA is an aminosalicylate, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. This includes prevention of further gastrointestinal tract absorption by emesis and, if necessary, by gastric lavage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.
DOSAGE AND ADMINISTRATION: The recommended dosage for the induction of remission and the symptomatic treatment of mildly to moderately active ulcerative colitis is 1g (4 PENTASA 250 mg capsules or 2 PENTASA 500 mg capsules) 4 times a day for a total daily dosage of 4g. Treatment duration in controlled trials was up to 8 weeks.

HOW SUPPLIED
PENTASA controlled-release 250 mg capsules are supplied in bottles of 240 capsules (NDC 54092-189-81); and blister packs of 80 capsules (NDC 54092-189-80). Each green and blue capsule contains 250 mg of mesalamine in controlled-release beads. PENTASA controlled-release capsules are identified with a pentagonal starburst logo and the number 2010 on the green portion and PENTASA 250 mg on the blue portion of the capsules.
PENTASA controlled-release 500 mg capsules are supplied in bottles of 120 capsules (NDC 54092-191-12); and blister packs of 80 capsules (NDC 54092-191-80). Each blue capsule contains 500 mg of mesalamine in controlled-release beads. PENTASA controlled-release capsules are identified with a pentagonal starburst logo and PENTASA 500 mg on the capsules.
Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Manufactured for **Shire US Inc.**, 725 Chesterbrook Blvd., Wayne, PA 19087, USA
© 2004 Shire US Inc.
Licensed U.S. Patent Nos. B1 4,496,553 and 4,980,173. Licensed from Ferring A/S, Denmark
189 0107 007A
XXXXXXX
Rev. 07/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-049/S015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-049 / SCS-015 **Stamp Date**: 3/8/04

Trade Name: Pentasa® Extended Release Capsules, 250 mg

Active Ingredient: Mesalamine

Sponsor: Shire Pharmaceutical Development Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Prior-Approval Supplement – Addition of New Dose Strength

Background

Pentasa® Extended Release Capsule, 250 mg, an aminosalicylate anti-inflammatory product, is currently approved in the US for the treatment of mildly to moderately active ulcerative colitis. The recommended dose of Pentasa® is 1 g (4 Pentasa capsules) four times a day for a total daily dose of 4 g.

The current submission provides for the addition of a new 500 mg dose strength of Pentasa® Extended Release Capsule. The manufacturing and testing process used for the additional strength are essentially identical to the currently approved 250 mg Capsule. In addition, the 500 mg strength is produced by

In support of the addition of the new 500 mg dose strength of Pentasa® Extended Release Capsule, the sponsor has submitted comparative dissolution profiles (dissolution method with f_2 values for the new 500 mg dose strength and the currently approved 250 mg Capsule (see attachment 2).

Based on the comparative dissolution profiles, the new Pentasa® Extended Release Capsule, 500 mg is equivalent to the currently approved 250 mg Pentasa® Extended Release Capsule.

Reviewer's Recommendations

NDA 20-049/SCS-014 providing for the addition of a new 500 mg dose strength of Pentasa® Extended Release Capsule has been reviewed by the Office of Clinical

Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and from a CPB perspective, it is found to be **acceptable**.

Attachment 1

Table 3 Pentasa® (mesalamine) Controlled Release Capsules 500 mg Ingredients: Comparison with 250 mg Capsules

INGREDIENT	Content (mg)/ 500 mg Capsule	% W/W (500 mg Capsule)	%W/W (250 mg Capsule)
Active Blend			
Mesalamine	500.0		
Talc, USP			
Colloidal Silicon Dioxide, NF			
White Wax, NF			
Ethylcellulose, NF			
Castor Oil, USP			
Stearic Acid, NF			
Ethylcellulose, NF			
Hydroxypropyl Methylcellulose, USP 2910			
Acetylated Monoglyceride			
Total Capsule Fill Weight		100.0	100.0

* Does not appear in the final product.

Note: The % w/w for the 250 mg and 500 mg capsules are identical if the

Attachment 2

Chromatographic Conditions:

- Flow rate:
- Injection volume:
- Autosampler Temperature:
- UV detector wavelength: nm
- Linear Program:

Time	%A	%B
0		
30		
35		
37		
52		

3.5.2.3 Dissolution -

The dissolution profile of mesalamine is determined in pH buffer using a USP Type 2 *dissolution apparatus* at RPM. Quantitative determination is made by UV spectrophotometry at a range of nm.

Equipment, Reagents, and Operating Parameters

- (USP Type 2, paddles)
- , pH , Diluent and dissolution media)
- Rotation speed: RPM
- Temperature: 37 ± 0.5°C
- Media volume: 900 mL
- Total time: 8 hours
- Sampling points: 60, 120, 240, and 480 minutes
- Detector: UV at nm (range nm)
- Flow cell:
- Blank solution: Empty capsule dissolved in 900 mL media

3.5.3 Methods Validation

The test methods described in the sections above have been validated and have been shown to be appropriate for their intended use. Copies of Method Validation reports for and are provided in Appendices 10, 11, and 12.

Dissolution Profile Comparability Study Protocol for Pentasa 500 mg Capsules,

Protocol Number: 04 - 003A

Appendix A

Analytical Results for Comparability Study

Table: 3 Similarity Factor (f_2) Results

Comparability results between unchanged product and product changed					
Sampling Time Point (hour)	Changed Product (SUMI) Batch #: 0b403009Z Mean % Drug Release	Unchanged Product (Marketed Product) Mean % Drug Release	% Different	f_2	Disposition
		Batch#: 3H7258			
1	[redacted]	[redacted]		62	☑ Pass ☐ Fail
2					
4					
6					
8					
		Batch#: 3H7257			
1	[redacted]	[redacted]		77	☑ Pass ☐ Fail
2					
4					
6					
8					
10					
		Batch#: 3H7259			
1	[redacted]	[redacted]		66	☑ Pass ☐ Fail
2					
4					
6					
8					
10					
Acceptance Criteria	% Difference NMT — A calculated f_2 value between 50 and 100				
SUMI Notebook References	NB 40004/5 p. 28-30				

Table 12 Registration Specifications for Pentasa® (mesalamine) Controlled Release Capsules 500 mg

Test Name	*Method*	*Specification*
Description	Visual	Size Body: light blue opaque Cap: light blue opaque Black printing: PENTAGON SYMBOL logo on the body and the "PENTASA/500 mg" on the cap containing
Identification		*Positive for mesalamine*
Assay – Mesalamine		*Label Claim: 500 mg/capsule* *Release Specification* *mg/capsule*
Decomposition Products		*Single Peak area NMT* mesalamine peak area *Total peak area NMT* of mesalamine peak area
Drug Release	L_1 Time Averages Individual 1 hour 2 hours 4 hours 8 hours NLT NLT L_2, L_3 Time Averages Individual 2 of 24 Range 1 hour 2 hours 4 hours 8 hours NLT NLT % NLT	**L_1 (Number tested = 6)** No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time **L_2 (Number tested = 6)** The average value of the 12 units (L_1 + L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time. **L_3 (Number tested = 12)** The average value of the 24 units (L_1 + L_2 + L_3) lies within each of the stated ranges and is not less than the stated amount at the final test time; not more than 2 of 24 units are more than 10% of labeled content outside each of the stated ranges; and not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of the labeled content outside each of the stated ranges or more than 20% of the labeled content below that stated amount at the final test time.

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/s/

Suliman Alfayoumi
6/30/04 01:18:55 PM
BIOPHARMACEUTICS

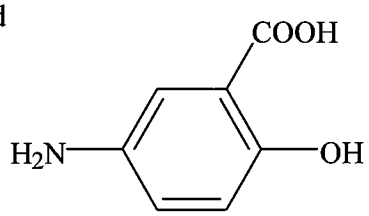
Suresh Doddapaneni
6/30/04 02:04:24 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-049/S015

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW # 1	1. Organization: HFD-180	2. NDA number: 20-049	
3. Name and Address of Applicant (City & State): Shire Pharmaceutical Development Inc. 1801 Research Boulevard Suite 600 Rockville MD 20850		4. AF Number:	
		5. Supplement(s)	
6. Name of Drug: Pentasa	7. Nonproprietary Name: Mesalamine	Numbers SCS-015	Dates March 08, 2004
8. Supplement Provides for: Pentasa (mesalamine) Controlled-Release Capsules 500 mg, manufactured at Shire US manufacturing Inc. (SUM), as an additional strength of Pentasa (mesalamine) Controlled-release Capsules.		9. Amendments and Other (Reports, etc.) Dates:	
10. Pharmacological Category: Aminosalicylate anti-inflammatory agent	11.How Dispensed: RX _X OTC	12. Related DMF(s):	
13.Dosage Form and Route of Administration Controlled Release Capsules - Oral	14. Potency: 250mg		
15. Chemical Name and Structure: 5-amino-2-hydroxybenzoic acid  		16. Records and Reports:	
		Current Yes _X_ No	
		Reviewed Yes _X_ No	

Comments:
The Clinical Pharmacology and Biopharmaceutics review for this supplement, June 30, 2004, indicated that the application is acceptable.
CC:
NDA 20-049/S-015
HFD-180/Div File
HFD-181/CSO/B.Scrorggs
HFD-180/B.Justice
HFD-180/Al-Hakim
HFD-180/L.Zhou
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17. Conclusions and Recommendations:
It is recommended that the Regulatory Health Project Manager issue an APPROVED letter for this supplement.

19. Reviewer	
Name: Ali Al-Hakim, Ph.D.	Date Completed: 07/02/04

Review Notes

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-049
S015

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/s/

Ali Al-Hakim
7/2/04 02:25:56 PM
CHEMIST

Liang Zhou
7/2/04 03:26:23 PM
CHEMIST
Approval recommnedation. and Need Bob/Joyce signature

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-049/S015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Numbers:	**NDA 20-049/SCS-015 for Pentasa® (mesalamine) CR Capsules, 250 mg**
Sponsor:	Shire Pharmaceutical Development, Inc.
Submission Date:	March 8, 2004
Receipt Date:	March 8, 2004

Material Reviewed

Background and Summary Description:

NDA 20-049 for Pentasa® (mesalamine) CR Capsules, 250 mg was approved May 10, 1993 for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

The currently approved labeling was approved with Supplement S-006 on September 10, 1999.

NDA 20-049/SCS-015 provides for the addition of a 500 mg capsule requiring changes to the Title Header, Description, Dosage and Administration, and How Supplied sections of the package insert, as well as providing for changes to the Storage, Sponsor address, Licensing Information, Copyright, and Revision date sections.

Review
Deletions are shown as ~~strikeouts~~ and additions are shown as double underlines. The following revisions were noted.

A. Package insert
The submitted draft package insert, identified (coded 189 0117 005) was compared to the package insert identified (189 0107 002, Rev. 6/99), approved with S-006 on September 10, 1999.

1. The Product Name and Strength section now reads:

"~~Prescribing Information as of June 1999~~
PENTASA®
(mesalamine)
Controlled-Release Capsules 250 mg and 500 mg
Prescribing Information as of June 1999 Rx."

Comments: The 500 mg strength has been added and is acceptable. However the "prescribing information as of date" should be updated from June 1999 to XXXX 2004 pending supplement action and should be communicated to the firm. The symbol "℞", has been added in the spirit of compliance with the Labeling Final Rule effective April 2, 2002 eliminating the need to use the phrase "Caution: Federal law prohibits dispensing without a prescription" However, the Rule states that the new statement must appear as "℞ only" or "Rx only" therefore this revision is not acceptable and should be communicated to the firm.

2. In the DESCRIPTION section, a third paragraph has been added and reads:

> "Each 500 mg capsule contains 500 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains FD&C Blue #1, gelatin, titanium dioxide, and other ingredients."

Comment: This is an acceptable addition per the chemistry, manufacturing and controls review.

3. In the DOSAGE AND ADMINISTRATION section, this section now reads:

> "**DOSAGE AND ADMINISTRATION:** The recommended dosage for the induction of remission and the symptomatic treatment of mildly to moderately active ulcerative colitis is 1g (4 PENTASA 250 mg capsules or 2 PENTASA 500 mg capsules) 4 times a day for a total daily dosage of 4g. Treatment duration in controlled trials was up to 8 weeks."

Comment: This is an acceptable revision per the chemistry, manufacturing and controls review.

4. In the HOW SUPPLIED section, a second paragraph has been added and reads:

> "PENTASA controlled-release 500 mg capsules are supplied in bottles of 120 capsules (NDC 54092-191-12), and blister packs of 80 capsules (NDC 54092-191-80). Each blue capsule contains 500 mg of mesalamine in controlled-release beads. PENTASA controlled-release capsules are identified with a pentagonal starburst logo and PENTASA 500 mg on the capsules."

Comment: This is an acceptable revision.

5. Other changes are reflected in the Address, Licensing, Copyright, and Identifier and read as follow:

"~~Prescribing Information as of June 1999~~
~~Manufactured for Roberts Laboratories Inc., a subsidiary of ROBERTS PHARMACEUTICAL COPR., Eatontown, NJ 07724, USA~~
~~Copyright ©1999 Roberts Laboratories Inc.~~

Shire US Inc.
One Riverfront Plaza
Newport, KY, USA

Licensed U.S. Patent Nos. B1 4,496,553 and 4,980,173

Licensed from Ferring A/S, Denmark

Copyright © 2004 Shire US Inc. Rev. xx/2004

189 0117 ~~002~~005 ~~50019193~~xxxxxxxx."

Comment: These are acceptable revisions.

B. Sample Package Carton (contains #8 blister-packaged capsules)
The submitted draft sample package carton, identified as Pent500/8cart (coded 191 0834 001, Rev. 07/03) was compared to the sample package carton (contains #16 x 250 mg blister-packaged capsules, identified (coded 189 1634 003, Rev. 02/02), submitted in the July 28, 2003 annual report.

The quantity on the front panel has been revised to read as : "~~16~~ 8 CAPSULES."
The side panel continues to read as: "250 mg".

Comment: The 250 mg on the side panel should be updated to read as "500 mg". The chemistry, manufacturing, and controls review notes this as well as recommending that the word "capsules" should be placed next to the established name. These recommended changes will be communicated in the action letter to the sponsor

C. Carton (contains #80 blister packaged capsules)
The submitted draft carton, identified as Pent80/500Cart (coded 191 8004 001, Rev. 07/03) was compared to the carton (contains #80 x 250 mg capsules) identified (coded 189 8004 002, Rev. 02/02), submitted in the July 28, 2003 annual report.

The NDC number has been revised for the new strength and package.

Comment: This is an acceptable change.

D. Container Label (#120 capsule-size bottle)
The submitted draft container label, identified as Pent500/120s8/11 (coded 191 1201 001 Rev 07/03 was compared to the bottle label (contains #240 x 250 mg capsules) identified (coded 189 8101 003, Rev. 02/02, submitted in the July 28, 2003 annual report.

The NDC number has been revised for the new strength and package. The container size has been revised as "~~240~~ 120 CAPSULES". The new strength, 500 mg is noted in the "each capsule contains line".

Comment: These are acceptable changes.

E. Blister Label
The submitted draft blister label (coded 191 8008 001, Rev 08/03) was reviewed and reads

"PENTASA®
(mesalamine)
Controlled-Release Capsules
1 Capsule 500 mg each
Lot xxxxxxxxxxxxxxx
Exp. Date
Shire US Inc.
191 8008 001 Revised 8/03."

Comment: This blister label is acceptable.

Conclusions

- Package Insert: The "prescribing information as of date" should be updated from June 1999. The "Rx only" should be added to the package insert in its entirety.
- Sample Pack Carton: The chemistry, manufacturing and controls review dated July 2, 2004 states that the 250 mg on the side panel should be updated to read as 500 mg.
- Carton (contains #80 x 500 mg blister packaged capsules): The changes are acceptable.
- Container Label (#120 x 500 mg capsule bottle): The changes are acceptable.
- Blister Label: The blister label is acceptable.

- The word "capsules" should follow the words "controlled-release" wherever the established name appears on all carton sizes.

The chemistry, manufacturing and controls review recommends approval. The recommended changes to the label should be conveyed.

An action letter recommending approval and conveying the recommended changes above will be drafted.

Betsy Scroggs, Pharm.D.
Consumer Safety Officer

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

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/s/

Betsy Scroggs
7/7/04 02:23:22 PM
CSO

Brian Strongin
7/8/04 10:23:20 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-049/S-015

Shire Pharmaceutical Development Inc.
Attention: Raj Kishore, Ph. D.
Senior Director, Regulatory Affairs
1801 Research Blvd., Suite 600
Rockville, MD 20850

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pentasa® (meslamine) Capsule, 250 mg

NDA Number: 20-049

Supplement number: #015

Date of supplement: March 8, 2004

Date of receipt: March 8, 2004

This supplemental application provides for the addition of a new strength (500 mg capsule).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 7, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 8, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service or Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Gastrointestional and Coagulation Drug Products
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Please contact me if you have any questions by calling me at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm. D.
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products, HFD 180
Center for Drug Evaluation and Research

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/s/

Betsy Scroggs
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