CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 020049/S-027

Trade Name: **PENTASA**

Generic Name: **Mesalamine**

Sponsor: **Shire Development LLC**

Approval Date: August 5, 2015

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020049/S-027

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020049/S-027

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20049/S-027

SUPPLEMENT APPROVAL

Shire Development LLC
Attention: Jennifer Pavillard
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Ms. Pavillard:

Please refer to your Supplemental New Drug Application (sNDA) dated and received January 15, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pentasa (mesalamine) Controlled-Release Capsules.

This "Prior Approval" supplemental new drug application proposes to revise the package insert to support the option of sprinkling the contents of the Pentasa capsule onto applesauce or yogurt.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

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 Heather Buck, Regulatory Project Manager, at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

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

/s/

JOYCE A KORVICK
08/05/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020049/S-027

LABELING

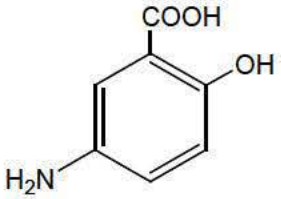
PENTASA®
(mesalamine)
Controlled-Release Capsules 250 mg and 500 mg
Prescribing Information as of 8/2015
Rx only

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.

Parameter Evaluated	Clinical Trial UC-1			Clinical Trial-UC-2		
		PENTASA			PENTASA	
	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, especially during the initial phase of treatment. Mesalamine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.

Interference with Laboratory Tests

Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection, because of the similarity in the chromatograms of normetanephrine and mesalamine's main metabolite, N-acetylaminosalicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

Drug Interactions

There are no data on interactions between PENTASA and other drugs.

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 in 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/M²) and rabbits at doses of 800 mg/kg/day (6856 mg/M²) 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.

No controlled studies with PENTASA during breast-feeding have been carried out. Hypersensitivity reactions like diarrhea in the infant cannot be excluded.

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® (mesalamine)-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 hematological, 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 moniliasis, 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 the PENTASA brand of 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 enzymes (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), hepatitis, 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.

Other: Postmarketing reports of anaphylactic reaction, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), pneumonitis, granulocytopenia, systemic lupus erythematosis, acute renal failure, chronic renal failure and angioedema have been received in patients taking PENTASA.

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.

PENTASA capsules may be swallowed whole, or alternatively, the capsule may be opened and the entire contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. The capsules and capsule contents must not be crushed or chewed.

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

HOW SUPPLIED

PENTASA controlled-release 250 mg capsules are supplied in bottles of 240 capsules (NDC 54092-189-81). 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 or S429 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). 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 or S429 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
PENTASA is a registered trademark of Ferring B.V.

Rev. 8/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020049/S-027

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW

Office of New Drug Products

Application No.:	NDA 20049 Supplement 027	**Primary Reviewer:** Vincent (Peng) Duan, Ph.D.	
Submission Date:	08/20/2014		
Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)	**Acting Quality Assessment Lead:** Tien-Mien Chen, Ph.D. **Acting Branch Chief:** Tapash Ghosh, Ph.D.	
Applicant:	Shire		
Trade Name:	Pentasa	**Date Assigned:**	Reassigned on Dec 22, 2014
Generic Name:	mesalamine	**Date of Review:**	06/15/2015
Indication:	For the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis	**Type of Submission: Prior Approval Labeling Supplement**	
Formulation/strengths:	250 mg and 500 mg ER capsules		
Route of Administration:	Oral		

Summary

Submission: NDA 20049 supplement S027 was for Pentasa (mesalamine) Controlled- Release Capsules (NDA 20-049) owned by Shire Development LLC (Shire). The original NDA was approved on 10 May 1993 for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

The Applicant submitted this PAS to provide the supportive information for the proposed changes made to the labeling under the Dosage and Administration section of the current United States Prescribing Information (USPI), and to give patients the option of sprinkling the contents of the capsule onto soft foods for patient convenience (e.g., those patients who may have difficulty swallowing intact capsules).

The Applicant's proposed labeling revisions because of this change is as follows:

> *PENTASA capsules may be swallowed whole, or alternatively, the capsule may be opened and the entire contents sprinkled in to a small quantity of* (b) (4) *applesauce, yoghurt* (b) (4) *and consumed immediately.* (b) (4)

The capsules and capsule contents must not be crushed or chewed.

Review: Biopharmaceutics review will focus on the review of comparative dissolution studies from the Applicant comparing the dissolution profiles between the intact capsule (Pentasa Controlled-Release Capsules) and the contents as the controlled release (CR) beads of the Pentasa Controlled-Release Capsules. Both 250 mg and 500 mg strengths were tested in vitro. The contents of the capsules were sprinkled on representative food or vehicle and the in vitro stability of the capsule contents in the foods was studied using the approved dissolution methodology outlined in NDA 20049.

The dissolution profiles of intact capsules of both strengths are comparable to the controlled released (CR) beads after being exposed to the food or vehicle tested ((b) (4) , yogurt, and applesauce) for 5 min and 60 min. The drug releases under different conditions are also conforming to the approved dissolution acceptance criteria.

Recommendation:

From the Biopharmaceutics perspectives, this NDA supplement is reviewed and found acceptable, therefore, it is recommended for approval. The Applicant identified applesauce and yogurt as the specific permitted soft-foods in the proposed label. However, (b) (4) would not be considered as a soft food.

On May 6, 2015, the Applicant agreed with our changes in the label as follows:

> *PENTASA capsules may be swallowed whole, or alternatively, the capsule may be opened and the entire contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. The capsules and capsule contents must not be crushed or chewed.*

Signature: **Signature:**

06/22/15 06/22/15

Vincent (Peng) Duan, Ph.D. Tien Mien Chen, Ph.D.

Biopharmaceutics reviewer Acting Biopharmaceutics Quality Assessment Lead

Office of New Drug Products Office of New Drug Products

Cc. TGhosh ; PSeo

Background

Pentasa (mesalamine) Controlled- Release Capsules (NDA 20-049) owned by Shire Development LLC (Shire) was approved on 10 May 1993 for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

Current Submission

This NDA supplement is a prior approval-labeling supplement (PAS) seeking approval for the option of sprinkling the contents of the Pentasa capsule onto food (b) (4). This PAS is also referenced to the Agency's Meeting Request Written Responses Only (WRO) dated 28 May 2014 in response to Shires questions contained in the 14 March 2014 (sequence 0019) background package.

In the WRO to the Applicant, the Agency suggested the Applicant the followings to support the proposed updates to the Dosage and Administration section of the Pentasa label:

> *FDA Response: We do not agree with the information you plan to submit to support your proposed change to the Dosage and Administration Section of the label, allowing mixing of the capsule contents with soft foods for the purpose of administration to the patient.*
>
> *Because the granules are formulated as modified release granules, the release properties may differ from one food to another based on differences in the pH of the foods. You will need to specify which foods are acceptable based on the stability and dissolution data you submit. Alternatively, if you provide data to demonstrate that the stability and dissolution properties of the granules do not change in foods that cover a broad pH range, it may be possible to allow the use of "soft foods" in the label instead of identifying the specific permitted foods.*
>
> *After mixing the capsule contents with food and taking a sample for assay during the one hour period, you should follow the approved dissolution method for drug release testing and compare the dissolution profile with that of the intact drug product. The types, brands, and pH values of the food should be specified.*
>
> *In addition, in order to generate adequate sample size for each time point for meaningful/statistical calculation (mean ± standard deviation), it is recommended that the sample size be $n \geq 6$ per each time point/food vehicle*

A follow-up correspondence was also submitted to the Agency (June 9, 2014) and responded by the Agency (September 18, 2014). The advice received from the Agency in all aforementioned forums detailed the supportive Chemistry, Manufacturing, and Control (CMC) data that would need to be provided. Specifically, the Agency recommended that the following supportive CMC data be submitted to support this labeling PAS:

1. Provide stability data to demonstrate that the drug does not degrade in the time period that the Sponsor would like to specify in the USPI. Even if the instructions call for sprinkling onto food and consuming immediately, at least one hour of stability data in the proposed food vehicles will be required.

2. Using the dissolution method that is approved under Pentasa® NDA (20-049), demonstrate that comparable dissolution profiles are obtained between the intact capsule and for the product dispersed in the food vehicle.

In response to the Agency's requirement, the Applicant provides the Agency with the requested comparative dissolution profiles between the intact capsule (Pentasa® Controlled-Release Capsules, 250mg and 500mg) and the contents of the Pentasa® Controlled-Release Capsules, 250mg and 500mg (also referred to as CR beads) sprinkled on representative food vehicles and the in vitro stability of the capsule contents in the foods was studied using the approved dissolution methodology outlined in NDA 20049. Reference is made to 3.2.P.8.1 and 3.2.P.8.3 that contain the stability results that demonstrate the CR beads do not degrade in the presence of soft foods for up to 60 minutes.

Biopharmaceutics Review:

Biopharmaceutics review will focus on the review of comparative dissolution studies from the Applicant comparing the dissolution profiles between the intact capsule (Pentasa Controlled-Release Capsules, for both 250 mg and 500 mg) and the contents of the Pentasa Controlled-Release Capsules, 250 mg and 500 mg, respectively (referred to as CR beads) sprinkled on representative food vehicles. The in vitro stability of the capsule contents in the foods was studied using the approved dissolution methodology outlined in NDA 20049.

Comparative dissolution results

1. Dissolution methods and specifications

The current specification for mesalamine controlled-released capsules 250 mg/ 500 mg is as shown in Table 1.

Table 1a: Specifications for Pentasa Capsules, 250mg

Test	Method	Acceptance Criteria
Appearance (release and shelf life)	(b) (4)	(b) (4)
Identification (release only)		
Uniformity of Dosage Units (release only)	Current USP <905>	Meets USP <905> for weight variation
Assay – Mesalamine (release and shelf life)	(b) (4)	(b) (4)

Decomposition Products (release and shelf life)	(b) (4)	(b) (4)
Drug Release [1] (release and shelf life)		
Residual Solvents (release only)		

Table 1b: Specifications for Pentasa Capsules, 500mg

Test	Method	Acceptance Criteria
Appearance (release and shelf life)	(b) (4)	(b) (4)
Identification (release only)		
Uniformity of Dosage Units (release only)	Current USP <905>	Meets USP <905> for weight variation
Assay – Mesalamine (release and shelf life)	(b) (4)	(b) (4)
Decomposition Products (release and shelf life)		

Drug Release [1] (release and shelf life)	(b) (4)
Residual Solvents (release only)	

The dissolution method is as following table:

Dissolution conditions	**Settings**
USP Apparatus	Type 2 Paddle at 100 rpm
Media	900 mL Phosphate Buffer (0.05 M), pH 7.5
Sampling Time Point	30, 60, 120, 240, and 480 min

This method is the current approved USP method for mesalamine extended release capsules. The acceptance criteria are as follows:

Time (hours)	**Amount dissolved**
1	(b) (4)
2	
4	
8	

2. Batches used in the dissolution profiles comparison

The reference samples Pentasa capsules 250 mg and 500 mg (intact capsules) used in the dissolution comparisons are the batches (Batch AD2742 for 250 mg, and Batch AD0661 for 500 mg) manufactured at approved manufacturing site (Patheon Manufacturing Serves LLC, formally known as DSM Pharmaceuticals Inc. (DPI)). The Applicant also used the same exact Pentasa capsules 250 mg and 500 mg as used for the intact reference material for the evaluation of the controlled release (CR) beads on the three tested food vehicles (applesauce, yogurt, (b) (4)).

3. Dissolution profiles comparison of intact capsules and capsules sprinkled to tested food vehicles

The Applicant tested the dissolution profiles comparison of intact capsules and capsules exposure to applesauce, yogurt, (b) (4) for 5 min and 60 min. The type, brand, and pH values of the tested foods are shown in Table 2:

Table 2: Type, Brand and pH value of the Foods		
Food Type	**Brand/Source**	**pH value [a]**
Applesauce, Plain	Mott's	Approximately pH 3.3
Yogurt, Plain	Dannon	Approximately pH 4.1
(b) (4)		

a Measured at the initial time of the test.

The dissolution profiles between Pentasa 250 or 500 mg (intact capsules) and the capsules contents (Pentasa 250 or 500 mg capsules) sprinkled onto soft foods are shown in Figure 1 and 2.

Figure 1: Dissolution Profiles Comparison between Pentasa® 250mg (Intact Capsules) and the Capsule Contents (Pentasa® 250mg Capsules) Sprinkled onto Soft Foods

Figure 2: Dissolution Profiles Comparison Between Pentasa® 500mg (Intact Capsules) and the Capsule Contents (Pentasa® 500mg Capsules) Sprinkled onto Soft Foods.

4. Similarity factor (f2) Calculation:

To demonstrate the similarity of dissolution profiles between intact capsules and CR beads after being exposed to different types of food for 5 min or 60 min, the Applicant also calculated f2 as Table 3 showed. These f2 values are consistent with the reviewer's own calculations and all of them are higher than 50, therefore, they showed similar dissolution profiles and CR beads are considered stable in vitro in the presence of soft foods for up to 60 minutes. Please see stability results in Module 3.2.P.8.1 and 3.2.P.8.3 for details.

Table 3. Dissolution Profiles Comparisons

Reference product: Pentasa CR Intact Capsules, 250 mg (n=12)		
Test conditions (foods, exposure time)	**f2 values provided by the Applicant**	**f2 values from the reviewer's own calculations**
(b) (4)		
Yogurt, 5 min	60	60
Yogurt, 60 min	61	61
Applesauce, 5 min	76	76
Applesauce, 60 min	71	71
Reference product: Pentasa CR Intact Capsules, 500 mg (n=12)		
(b) (4)		

Yogurt, 5 min	73	73
Yogurt, 60 min	82	82
Applesauce, 5 min	86	86
Applesauce, 60 min	83	83

Overall reviewer assessment

All the in vitro drug release either from intact capsules or from CR beads after being exposed to different types of food or vehicle for 5 min or 60 min meet the dissolution specifications per the USP <724> criteria for L1 of 5-25% dissolved at 1 hour; 30-50% dissolved at 2 hours; 60-90% dissolved at 4 hours; and not less than (NLT) 85% dissolved at 8 hours.

The similarity of drug release from CR beads after being exposed to the test food or vehicle for 5 min or 60 min when compared to that of intact capsules demonstrates that the drug is considered stable in vitro when mixed the foods up to 1 hr.

The foods or vehicle tested here applesauce, yogurt, (b) (4) covered the pH from (b) (4). However, (b) (4) is not deemed as a soft food per the compiled list as US FDA/ CFSAN – "Approximate pH of Foods and Food Products"*

* http://foodscience.caes.uga.edu/extension/documents/FDAapproximatepHoffoodslacfphs.pdf.

Therefore, the actual soft-food vehicles tested here were only applesauce and yogurt with pH 3.3 and 4.1, respectively and (b) (4) should not be stated as a soft food in the proposed label. A general term of "soft food" could not be used.

Changes in the label as follows are recommended to the Applicant on April 27, 2015:

> *PENTASA capsules may be swallowed whole, or alternatively, the capsule may be opened and the entire contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. The capsules and capsule contents must not be crushed or chewed.*

On 5/6/2015, the Applicant accepted above changes in label.

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/s/

PENG DUAN
09/16/2015

TIEN MIEN CHEN
09/16/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020049/S-027

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Review:	March 10, 2015
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 20049/s-027
Product Name and Strength:	Pentasa (mesalamine) controlled-release capsules 250 mg and 500 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Shire
Submission Date:	January 15, 2015
OSE RCM #:	2015-194
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

This review is in response to the request from the Division of Gastroenterology & Inborn Error Products (DGIEP) for DMEPA to review the proposed labeling changes to the prescribing information (PI) of Pentasa. Shire submitted their proposed labeling changes on January 15, 2015 for NDA 20049/s-027.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	N/A-D
ISMP Newsletters	E
Other	N/A-F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Pentasa controlled-release capsules were originally approved on May 10, 1993. On January 15, 2015 Shire submitted proposed labeling changes to the PI of Pentasa. Specifically, Shire has proposed text to add to the dosage and administration section of the PI to reflect the ability of the patient to now open the capsule and sprinkle the contents in certain foods (b) (4) to then be immediately swallowed. We performed a risk assessment of the currently marketed product, and the proposed labeling changes for any areas that may potentially lead to medication errors.

We conducted a search of the FDA Adverse Event Reporting System (FAERS), and the Institute for Safe Medication Practices (ISMP) newsletters database. Our FAERS search for Pentasa resulted in one relevant case, which involved improper administration of Pentasa by administering only a portion of the capsule contents when mixed with a certain food. A FAERS search was also conducted for Creon because the currently approved and marketed PI for Creon includes a statement similar to the proposed addition to the Pentasa PI. This FAERS search resulted in two relevant cases involving improper technique and instructions when

administering capsule contents. Our ISMP Newsletter search resulted in no relevant articles and/or cases to this review.

Through our risk assessment and evaluation of the submitted materials, we find the proposed labeling changes appropriate.

4 CONCLUSION & RECOMMENDATIONS

We conclude the sponsor's proposal to add the submitted text to the dosage and administration section of the Pentasa PI is appropriate.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pentasa that Shire submitted on January 15, 2015.

Table 2. Relevant Product Information for Pentasa	
Initial Approval Date	May 10, 1993
Active Ingredient	Mesalamine
Indication	For the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.
Route of Administration	Oral
Dosage Form	Capsule
Strength	250 mg; 500 mg
Dose and Frequency	The recommended dosage is 1g (4 PENTASA 250 mg capsules or 2 PENTASA 500 mg capsules) 4 times a day for a total daily dosage of 4g.
How Supplied	Pentasa controlled-release 250 mg capsules are supplied in bottles of 240 capsules. Pentasa controlled-release 500 mg capsules are supplied in bottles of 120 capsules.
Storage	Store at 25˚C (77˚F); excursions permitted to 15-30˚C (59-86˚F) [see USP Controlled Room Temperature].
Container Closure	See How Supplied.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on February 27, 2015 and March 3, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	**May 10, 1993 to February 27, 2015**
Product	**Pentasa**
Event (MedDRA Terms)	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

Our search identified 50 cases, of which one case described errors relevant to this review. This case involved the improper administration of Pentasa by inappropriately titrating the dose and administering only a portion of the capsule contents, after mixed with pudding, to the patient. The patient was ordered for a total of 1500 mg of Pentasa 2x/day. However, the first day the patient was to receive Pentasa at this dose, the caregiver only gave a portion of one 500 mg capsule to the patient, after mixing it in pudding. The next day the caregiver gave the full contents of one 500 mg capsule to the patient, after mixing it in pudding. The caregiver after two more days finally gave the correct dose of 1500 mg and the total contents of the capsules to the patient after mixing them in pudding.

We excluded 49 cases because they described issues unrelated to medication errors with this product/labeling supplement.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case and manufacturer control numbers for the cases relevant for this review.

- Case#: 10684665

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

B.4 Methods

Additionally, on March 3, 2015, a search was conducted via the same methods as above, but using the criteria listed below. The purpose of this search was to find any cases involving issues with the administration of capsule contents involving Creon, a drug product that already has a similar statement, to the proposed addition by Shire within the PI.

Table 4: FAERS Search Strategy	
Date Range	**April 30, 2009 to March 3, 2015**
Product	**Creon**
Event (MedDRA Terms)	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.5 Results

Our search identified 94 cases, of which two cases described medication errors relevant to this review. The first case involved a neonate patient and the caregiver dissolving one-fifth of capsule contents in 8.4% Sodium Bicarbonate solution prior to adding to breast milk or formula. The second case involved a patient being instructed by a physician to crush the capsule contents, mix with water, let stand for 30 minutes, and then mix with formula.

We excluded 92 cases because they issues unrelated to medication errors with this product/labeling supplement.

B.6 List of FAERS Case Numbers

- Case#: 10145855
- Case#: 9263464

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on February 27, 2015 using the terms, Pentasa, to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified one previous review[1], but this review is unrelated to the current labeling supplement.

[1] Bridges, T. Pentasa Post-Marketing Review Memo (NDA 20049). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2005 Mar 04. 2 p. OSE RCM No. (project number): 04-0323.

APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

N/A

D.2 Results

N/A

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on February 28, 2015 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Joint Commission Sentinel Event Alert; QAA Community; QAA Acute Care; PA Patient Safety Advisory; ISMP Canada Safety Bulletin; ISMP Nursing Newsletter; ISMP Community Newsletter; ISMP Acute Care Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: Pentasa

E.2 Results

There was one article found using the criteria above, but this article contained information that is not relevant to this review.

APPENDIX F.

F.1 Methods

N/A

F.2 Results

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Pentasa labels and labeling submitted by Shire on January 15, 2014.

- Prescribing Information

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MATTHEW J BARLOW
03/10/2015

KENDRA C WORTHY
03/11/2015

Division of Gastroenterology and Inborn Errors Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: 22049/S-027 (PAS)

Name of Drug: Pentasa (mesalamine) Controlled-Release Capsules

Applicant: Shire Development LLC

Labeling Reviewed

Submission Date: January 15, 2015

Receipt Date: January 15, 2015

Background and Summary Description:
This supplemental application proposes to revise labeling to support the option of sprinkling the contents of the Pentasa capsule onto food (b) (4). The label was last approved on December 16, 2013.

Review

The label last approved on December 16, 2013, was compared to the proposed label and found to be identical except for the proposed changes and spelling correction of "Stevens-Johnson syndrome" in the Postmarketing Reports section.

Recommendations

From a regulatory standpoint, this supplement is recommended for approval.

Regulatory Project Manager Date

Chief, Project Management Staff Date

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/s/

HEATHER G BUCK
05/04/2015

KEVIN B BUGIN
05/06/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020049/S-027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: OSE/DMEPA			Heather Buck, RPM, DGIEP	
DATE 1/28/2015	IND NO.	NDA NO. 20049/S-027	TYPE OF DOCUMENT Prior Approval Labeling Supplement	DATE OF DOCUMENT 1/15/15
NAME OF DRUG Pentasa (mesalamine)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 3/2/15

NAME OF FIRM: Shire

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We received a labeling supplement for Pentasa (20049 / S-027) on 1/15/15. The goal date is 7/15/15.

They propose revising the [redacted] (b) (4) ort the option of sprinkling the contents of the Pentasa capsule onto food [redacted]. This is based on our advice to the sponsor sent 11/23/13 (see DARRTS). Th [redacted] abel is attached. The sponsor submits quality data in support of this change (see SEQ 023 in submission: \\CDSESUB1\evsprod\NDA020049\020049.enx)

Clinical, CMC and Biopharm are involved. A team meeting will be scheduled for early March (tentatively 3/2/15 at 12PM).

Please send the reviewer name and any questions to Heather Buck.

SIGNATURE OF REQUESTER HGB	METHOD OF DELIVERY (Check all that apply) DARRTS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

HEATHER G BUCK
01/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 20049/S-027

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Shire Development LLC
Attention: Jennifer Pavillard
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Ms. Pavillard:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: NDA 20049

SUPPLEMENT NUMBER: S-027

PRODUCT NAME: Pentasa (mesalamine) Controlled-Release Capsules

DATE OF SUBMISSION: January 15, 2015

DATE OF RECEIPT: January 15, 2015

This supplemental application proposes to revise labeling to support the option of sprinkling the contents of the Pentasa capsule onto food (b) (4).

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 March 16, 2015, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be July 15, 2015.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HEATHER G BUCK
01/27/2015