CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204,412
Received Date(s)	12 November 2014
PDUFA Goal Date	11 September 2015
Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)
Reviewer Name(s)	Marjorie F. Dannis, M.D.
Review Completion Date	31 July 2015
Established Name	Mesalamine
Trade Name	Delzicol
Therapeutic Class	Aminosalicylate
Applicant	Warner Chilcott
Formulation(s)	Delayed release capsules, 400 mg
Dosing Regimen	Adults: Two 400 mg capsules three times daily for the treatment of mildly to moderately active ulcerative colitis 1.6 g daily Pediatrics: the recommended total daily dosage of Delzicol is weight-based (up to maximum of 2.4 grams per day) divided into two daily doses for a duration of 6 weeks
Indication(s)	Treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older
Intended Population(s)	Pediatrics and adults with ulcerative colitis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted data are adequate to support the recommendation of US marketing approval for Delzicol 400 mg delayed release capsules (WC3079) for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

The outstanding PREA PMR (2011-1) (shown below) for Delzicol 400 mg delayed release capsules is considered fulfilled.

> 2011-1 A randomized, double-blind study in pediatric patients ages 5 to 17 years with ulcerative colitis using an age-appropriate formulation to evaluate the pharmacokinetics, safety, and clinical response of pediatric patients undergoing six weeks of oral mesalamine therapy. The study should compare at least two different dose levels of mesalamine and enroll at least 40 pediatric patients in each dosing arm.

1.2 Risk Benefit Assessment

Asacol 400 mg tablets were approved in 1992. Asacol and other oral mesalamine products are part of the current standard of care for the treatment of patients with ulcerative colitis (UC). Previously, there was a safety concern regarding the use of dibutyl phthalate (DBP) as an excipient in the formulation of Asacol 400 mg tablets. This led to the manufacturing of a reformulated product, Delzicol 400 mg capsules, wherein DBP was replaced with dibutyl sebacate. Subsequently, Delzicol was approved (February 1, 2013) for treatment of mildly to moderately active UC and for maintenance therapy in adults based on demonstration of bioequivalence with Asacol.

The indicated population for Asacol was altered to include pediatric patients ages 5 to 17 years old (for 6 weeks of treatment) based on data from pediatric studies with Asacol submitted in an efficacy supplement (approved October 18, 2013) to the Asacol NDA.

The indicated population for Delzicol was altered to include pediatric patients ages 12 to 17 years old (for 6 weeks of treatment) based on data from pediatric studies with Asacol submitted in an efficacy supplement (approved April 28, 2014) to the Delzicol NDA.

It should be noted that the lower age limits differ between the Delzicol capsule and Asacol tablets because Delzicol is a larger capsule (size (b) (4) mm) compared to

Asacol (size (b) (4) mm) and young children (less than 12 years of age) may not be able to swallow the larger capsule.

The current application was in response to the PREA PMR 2011-1 (shown above) for Delzicol 400 mg delayed release capsules. Note that the current application proposes a new formulation of Delzicol (WC3079; a capsule containing four 100 mg tablets).

At the time of this review, the Clinical Pharmacology Reviewers and the ONDQA Biopharmaceutics Reviewers have concluded based on review of the results of the relative bioavailability study (PR-07513) and the results of dissolution studies that WC3079 400 mg capsules are comparable to Asacol 400 mg tablets. Therefore, it is expected that WC3079 capsules will be as effective as Asacol 400 mg tablets.

Review of the swallowability study (PR-00514) revealed that the majority of healthy children ages 5-11 (70%) were able to swallow eight placebo tablets in less than five minutes. In the youngest subgroup of children, ages 5-6, 40% were able to swallow the eight tablets; however, 45% were unable to swallow any tablets. However, if the study allowed for swallowing training of the healthy children or included children with chronic diseases, a larger percentage of the youngest children (ages 5-6) may have been successful in swallowing the tablets; data from the literature suggest that training on pill swallowing can be used for patients with chronic diseases.[1] The size of the 100 mg tablets (inside the capsule) is clearly smaller than the Asacol 400 mg tablet which is currently approved for patients down to 5 years of age. Thus, WC3079 appears to be an age appropriate formulation for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older. (b) (5)

Thus, it is anticipated that the benefits of WC3079 for the treatment of mildly to moderately UC outweigh the risks of WC3079 in the mildly to moderately active UC population.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarketing Requirements and Commitments

None

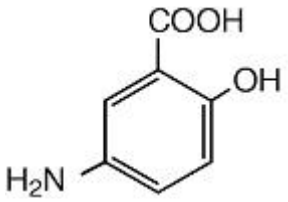
[1] Meltzer et al, 2006

2 Introduction and Regulatory Background

2.1 Product Information

Trade Name:	Delzicol
Generic Name:	Mesalamine (5-aminosalicylic acid; 5-ASA)
Code Name:	WC3079
Chemical Name:	5-amino-2-hydroxybenzoic acid

Structural formula:

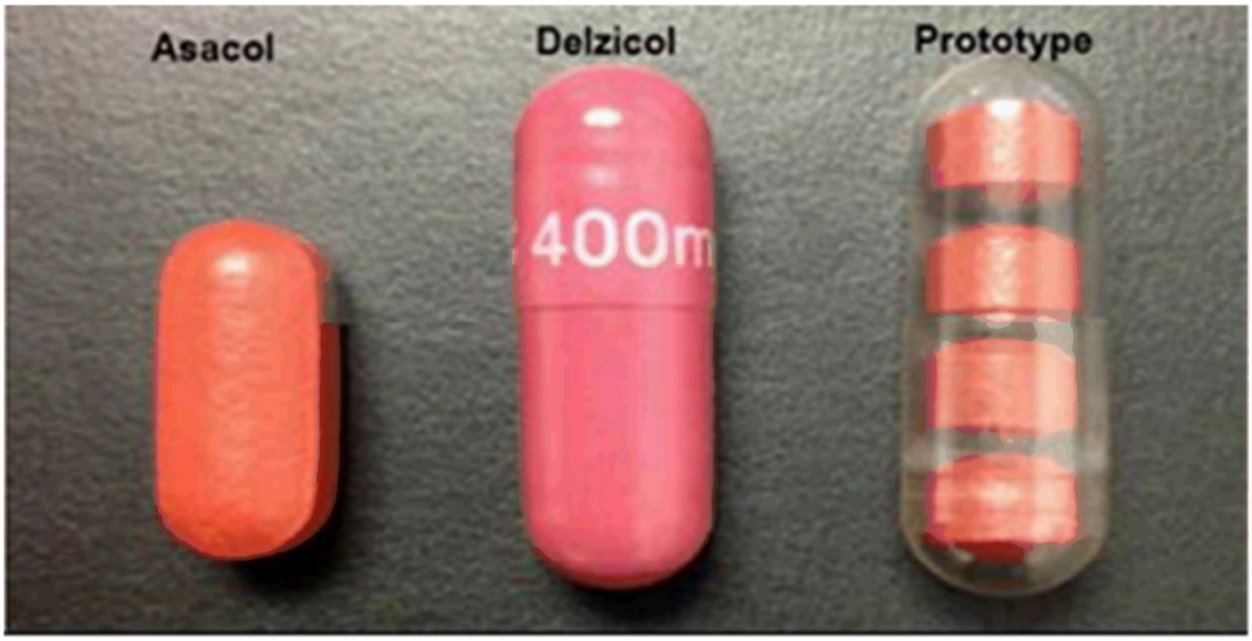


Therapeutic Class:	Aminosalicylate
Formulation:	Delayed-release capsules containing four 100 mg mesalamine delayed release tablets
Proposed indication:	Treatment of mildly to moderately active ulcerative colitis

The exact mechanism of action of mesalamine is unknown, but it appears to act topically rather than systemically. Oral mesalamine formulations have been accepted as a first line treatment for the induction and maintenance of remission of ulcerative colitis for over 40 years.

See Figure 1 below for a photographic representation of Asacol 400 mg, Delzicol 400 mg and the new formulation of Delzicol 400 mg (WC3079) respectively.

Figure 1: Asacol, Delzicol, and proposed new formulation of Delzicol



2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Products to Treat Ulcerative Colitis

Trade Name (generic)	Adults		Pediatrics	
	Induction/ treatment	Maintenance	Induction/ treatment	Maintenance
Apriso (mesalamine)		√		
Asacol (mesalamine)	√	√	√	√
Asacol HD (mesalamine)	√			
Azulfidine (sulfasalazine)	√	√		
Colazal (balsalazide)	√			
Dipentum (osalazine)		√		
Entocort (budesonide)	√	√*		
Humira (adalimumab)	√	√		
Lialda (mesalamine)	√	√		
Pentasa (mesalamine)	√			
Remicade (infliximab)	√	√	√	√
Rowasa (mesalamine)	√			
*Rectal cortisone and budesonide preparations	√			
Uceris	√			

* up to 3 months

2.3 Availability of Proposed Active Ingredient in the United States

Various oral and rectal mesalamine formulations are approved for marketing in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

The current labeling of other mesalamine products includes warnings and precautions regarding the risk of renal impairment, hepatic impairment, acute exacerbation of colitis, hypersensitivity reactions, and the risk of prolonged gastric retention in patients with outlet obstruction associated with the use of oral mesalamine products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2. Pre-submission Regulatory History, NDA 204412

Date	Regulatory Action(s)
January 15, 2013	Type C Meeting FDA informed Warner Chilcott that PREA required them to manufacture an age-appropriate pediatric formulation. In addition, they needed to conduct a palatability/ability to swallow study to determine acceptability of the proposed formulation (WC3079). FDA informed Warner Chilcott that they must justify that the WC3079 capsule can be bridged with Asacol
February 1, 2013	FDA approved Delzicol capsules, a dibutyl phthalate (DBP) free formulation based upon demonstration of bioequivalence to the reference product Asacol 400 mg tablets.
April 28, 2014	FDA approved Delzicol capsules for the treatment of mildly to moderately active ulcerative colitis for patients *12 years of age and older*.
November 11, 2014	Current sNDA submitted

2.6 Other Relevant Background Information

Mesalamine has been available worldwide for the treatment of inflammatory bowel disease (IBD) for more than 20 years and as the active component in sulfasalazine for more than 50 years.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was well-organized and easily navigable.

Since there were no efficacy studies included with this submission, the Office of Scientific Investigations (OSI) did not perform any clinical inspections. For further information, see Clinical Pharmacology review by Dr. Sandhya Apparaju.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all of the studies were conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human patients (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). All studies were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

3.3 Financial Disclosures

All investigators who participated in Study PR-07513 and Study PR-00514 certified as to not having a financial interest in the study. Therefore, financial disclosures are not applicable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

At the time of completion of this clinical review, the CMC review was unavailable. Thus, no conclusions regarding approvability of this application from a CMC perspective can be drawn.

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4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical studies were conducted in support of this NDA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The exact mechanism of action of mesalamine is unknown, but it appears to act topically rather than systemically as an anti-inflammatory agent.

4.4.2 Pharmacodynamics

Mesalamine is thought to exert its pharmacologic effects topically on the GI tract. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways (i.e., prostanoids), and through the lipoxygenase pathways (i.e., 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.

4.4.3 Pharmacokinetics

The Applicant submitted a relative bioavailability study (Study PR-07513) to study the pharmacokinetic profile and bioavailability of WC3079 capsules compared to Asacol 400 mg tablets. In addition, special dissolution studies over a range of pH values were conducted to determine if the dissolution profiles for WC3079 and Asacol 400 mg tablets were comparable.

At the time of this review, the Clinical Pharmacology and the ONDQA Biopharmaceutics teams have concluded that Delzicol 400 mg capsules (WC3079) are comparable to Asacol 400 mg tablets although bioequivalence was not demonstrated. See Clinical Pharmacology Review by Dr. Sandhya Apparaju and ONDQA Biopharmaceutics Review by Dr. Vincent Duan for complete details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Clinical studies Submitted for NDA 204412

Type of Study	Protocol Number / Report Number (eCTD section)	Study Objective(s)	Study Design and Type of Control	Test and Reference Product(s); Dosage Regimen; Administration Route	Number of Subjects Enrolled/ Completed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	PR-07513/ RR-02314 (5.3.1.2)	To assess the relative bioavailability of WC3079 mesalamine delayed-release capsules, 400 mg as compared to Asacol (mesalamine) delayed-release tablets, 400 mg To assess the affect of food on the bioavailability of WC3079 mesalamine delayed-release capsules, 400 mg	Open-label, randomized, single-dose, replicate treatment , 5-period, 4-sequence, 2-formulation crossover	WC3079 capsule; single dose; fasted oral WC3079 capsule; single dose; with food oral	160/146	Healthy male and female volunteers	5 single doses	Completed; Full
Other	PR-00514/ RR-09614 (5.3.5.4)	To characterize the swallowability of placebo tablets contained in WC3079 capsules by children 5 to 11 years old.	Open-label, single-dose study	WC3079 placebo capsules; single dose; oral	60/60	healthy male and female children ages 5 to 11 years old	Single dose	Completed; Full

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Study 00514 (Swallowability Study)

Study 00514 was a single-center, open-label, single-dose study conducted in 60 healthy children ages 5 to 11 years old. Approximately 20 subjects were to be enrolled in each of three cohorts stratified by age as follows:

- Ages 5 -6
- Ages 7- 9
- Ages 10 -11

All subjects were asked to swallow 8 placebo tablets as contained in two WC3079 placebo capsules.

Water was available to aid in swallowing the tablets. The caregiver was provided with the following instructions for administration:

"...the capsules may be carefully opened and the contents (tablets) swallowed. Ensure all capsule contents are swallowed and no tablets are retained in the mouth. The complete dose (8 tablets) should be swallowed. Swallow the tablets whole; do not cut, break, crush or chew the tablets."

Study PR-07513 (Relative Bioavailability Study)

Study PR-07513 was a single-center, open-label, randomized, single-dose, replicate treatment, 5-period, 4-sequence, 2-formulation crossover study conducted under in 160 healthy male and female volunteers. All subjects received Treatment 1 twice, Treatment 2 twice, and Treatment 3 once.

- Treatment 1: One Asacol (mesalamine) delayed-release tablet, 400 mg (fasted)
- Treatment 2: One mesalamine delayed-release capsule (Formulation WC3079-19F), 400 mg (fasted)
- Treatment 3: One mesalamine delayed-release capsule (Formulation WC3079-19F), 400 mg (with food)

Subjects were randomly assigned to one of four treatment sequences:

- Sequence A: Treatment 1–Treatment 3–Treatment 2–Treatment 1–Treatment 2
- Sequence B: Treatment 2–Treatment 1–Treatment 2–Treatment 3 –Treatment 1
- Sequence C: Treatment 1–Treatment 2–Treatment 3 –Treatment 1–Treatment 2
- Sequence D: Treatment 2–Treatment 1–Treatment 3–Treatment 2–Treatment 1

All study medications were orally administered with 240 mL (8 ounces) ambient-temperature water after an overnight fast of at least 10 hours, with at least 7 days between each treatment administration.

5.2 Review Strategy

The focus of this clinical review will be the swallowability study, Study PR-00514. This study was conducted to assess the ability of children who are 5 to 11 years old to swallow the eight 100-mg tablets contained in two WC3079 placebo capsules. In addition, the safety results of the relative bioavailability study, Study PR-07513, will be reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

Study PR-00514 (Swallowability Study)

Objective: To characterize the swallowability of placebo tablets contained in WC3079 capsules by children 5 to 11 years old.

Study Design and Plan Description: Study PR- 00514 was a single-center, open-label, single-dose study conducted in 60 healthy children ages 5 to 11 years old. Approximately 20 subjects were to be enrolled in each of three cohorts stratified by age as follows:

- Ages 5 -6
- Ages 7- 9
- Ages 10 -11

All subjects were asked to swallow 8 placebo tablets as contained in two WC3079 placebo capsules.

Water was available to aid in swallowing the tablets. The caregiver was provided with the following instructions for administration:
"...the capsules may be carefully opened and the contents (tablets) swallowed. Ensure all capsule contents are swallowed and no tablets are retained in the mouth. The complete dose (8 tablets) should be swallowed. Swallow the tablets whole; do not cut, break, crush or chew the tablets."

Study Population

Inclusion Criteria

- Healthy males or females of any race, aged 5 to 11 years inclusive
- Judged by the Investigator to be healthy on the basis of the pre-study medical history and screening procedures (physical examination)
- Have parent/guardian willing to assist in participation in the study, able to understand the study requirements, and willing to provide informed consent/assent

Exclusion Criteria

- Participation in any other investigational study drug trial in which receipt of an investigational study drug or device occurred within 28 days prior to study drug administration
- Hypersensitivity, idiosyncratic reaction, or intolerance to any component of the formulations
- A swallowing dysfunction caused either by anatomical or functional disorder (eg. cleft lip/palate, congenital anomalies of jaw, mouth, oral cavity and pharynx, tracheoesophageal abnormalities such as fistula or cyst)
- Any acute or chronic condition that, in the opinion of the Investigator, would limit the subject's ability to complete and/or participate in this clinical study

Treatments Administered

- All subjects were asked to swallow eight placebo tablets as contained in two placebo capsules.
- The caregiver was provided with the following instructions for administration:
    - "...the capsules may be carefully opened and the contents (tablets) swallowed. Ensure all capsule contents are swallowed and no tablets are retained in the mouth. The complete dose (eight tablets) should be swallowed. Swallow the tablets whole; do not cut, break, crush or chew the tablets."

Selection of Doses in the Study

The dosage regimen for Delzicol (mesalamine) for treatment of ulcerative colitis in adults is two 400-mg capsules to be taken three times daily (total daily dose of 2.4 g). For pediatric patients 12 years of age and older, the recommended total daily dose of Delzicol is weight-based (up to a maximum of 2.4 g/day). For the current study, each subject was asked to swallow two capsules containing eight placebo tablets (2x4 tablets/capsule).

Disposition of Subjects

- A total of 60 healthy, male and female children were enrolled into the study
- 60 subjects received study drug (placebo), and 60 subjects completed the study

Demographic and Other Baseline Characteristics

Subjects were exactly half male and half female, their median age was 8 with a range of 5 to 11 years. The median body mass index (BMI) was 16.8 kg/m^2 with a range of 13.8 to 26.8) kg/m^2 for the entire study population. See Table 4 below for further details of demographic and other baseline characteristics.

Table 4: Summary of Demographic and Other Baseline Characteristics

	Total (N =60)
Age (Years)	
n	60
Mean (SD)	8.2 (2.1)
Median	8.0
Min, Max	5, 11
Ethnicity	
Hispanic or Latino	23 (38.3%)
Not Hispanic or Latino	37 (61.7%)
Race	
American Indian or Alaska Native	0
Asian	0
Black or African American	12 (20.0%)
Multi Race	1 (1.7%)
Native Hawaiian or Other Pacific Islander	0
White	47 (78.3%)
Gender	
Female	30 (50.0%)
Male	30 (50.0%)
Height (cm)	
n	60
Mean (SD)	131.6 (12.0)
Median	130.0
Min, Max	109, 161
Weight (kg)	
n	60
Mean (SD)	32.2 (11.0)
Median	29.7
Min, Max	17.3, 61.4
BMI (kg/m2)	
n	60
Mean (SD)	18.1 (3.6)
Median	16.8
Min, Max	13.8, 26.8

Electronically copied and reproduced from CSR PR-00514 Table 14.1.2 pg 26

Swallowability Results

- **Overall, 42 (70%) of the children swallowed all 8 tablets.**
  - 7 -11yr olds
    - 85% (34/40) swallowed 8 tablets
    - 10% (4/40) swallowed 0 tablets (2 patients swallowed 1 tablet)
  - 5- 6 year olds
    - 40% (8/20) swallowed 8 tablets

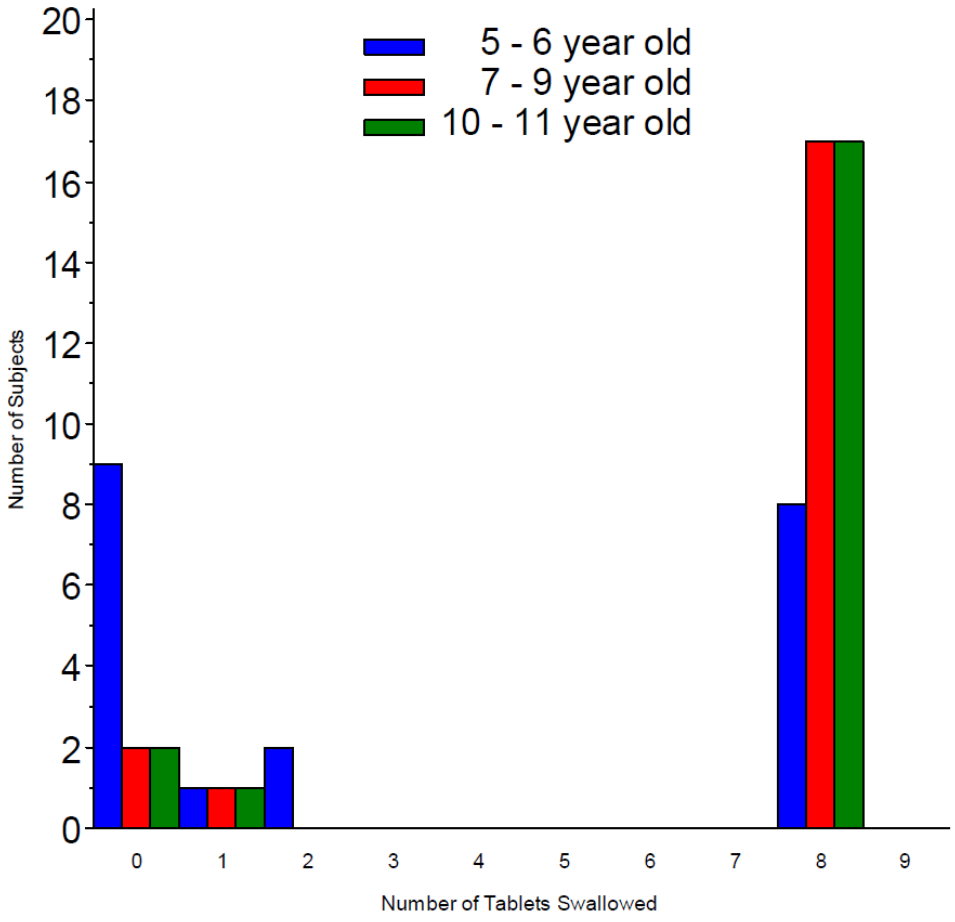
- 45% (9/20) swallowed 0 tablets
- (1 patient swallowed 1 tablet; 2 patients swallowed 2)

- **Most children swallowed the tablets in < 5 minutes**
  - only 3 children swallowed 1 additional tablet between 5 and 10 minutes after administration.

Swallowability by Age

Figure 2 below displays the results by in graphic format.

Figure 2: Swallowability by Age



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Discussion

The swallowability study was conducted in healthy children as opposed to children with a chronic illness. Data from the literature suggest that training on pill swallowing can be used for patients with chronic diseases.[2] The size of the 100 mg tablets (inside the capsule) is clearly smaller than the Asacol 400 mg tablet which is currently approved for patients down to 5 years of age. Therefore, the results above show that WC3079 may be an age appropriate formulation. (b) (5) [redacted].

Discussions of the relative bioavailability study and the special dissolution studies submitted in support of this application are found in the clinical pharmacology and biopharmaceutics reviews of Dr. Sandhya Apparaju and Dr. Vincent Duan, respectively.

6 Review of Efficacy

Efficacy Summary

No new clinical efficacy trials were submitted in support of this application. The current application provides results of a swallowability study, a relative bioavailability study (comparing the pharmacokinetic profile and bioavailability of WC3079 to Asacol 400 mg) and dissolution studies. According to the Clinical Pharmacology reviewers and the ONDQA Biopharmaceutics Reviewers, Delzicol WC3079 capsules are comparable to Asacol 400 mg tablets although bioequivalence was not demonstrated.

6.1 Indication

Proposed indication:

- Treatment of mildly to moderately active ulcerative colitis in patients ≥ 5 years of age

6.1.1 Methods

The Applicant submitted Study PR-00514, a study of the swallowability of WC3079 placebo capsules. The study was conducted in healthy pediatric subjects.

The Applicant submitted Study PR-07513, a relative bioavailability study comparing WC3079 (Delzicol 400 mg delayed release capsule new formulation) to the approved

[2] Meltzer et al, 2006

Asacol 400 mg delayed release tablet. The study was conducted in healthy male and female subjects.

6.1.2 Demographics

In Study PR-00514, subjects were exactly half male and half female, their median age was 8 with a range of 5 to 11 years. The median body mass index (BMI) was 16.8 kg/m^2 with a range of 13.8 to 26.8) kg/m^2 for the entire study population. See Table 4 above for further details of demographic and other baseline characteristics.

6.1.3 Subject Disposition

In Study PR-00514, a total of 60 healthy, male and female children were enrolled into the study. Sixty subjects received study drug (placebo), and 60 subjects completed the study

6.1.4 Analysis of Primary Endpoint(s)

See the Clinical pharmacology review by Dr. Sandhya Apparaju for details regarding the relative bioavailability study, PR-07513.

6.1.5 Analysis of Secondary Endpoints(s)

See the Clinical pharmacology review by Dr. Sandhya Apparaju for details regarding the relative bioavailability study, PR-07513.

6.1.6 Other Endpoints

See the Clinical pharmacology review by Dr. Sandhya Apparaju for details regarding the relative bioavailability study, PR-07513.

6.1.7 Subpopulations

See the Clinical pharmacology review by Dr. Sandhya Apparaju for details regarding the relative bioavailability study, PR-07513.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose-response trials were performed in support of this application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No efficacy studies were submitted in support of this application.

6.1.10 Additional Efficacy Issues/Analyses

No efficacy trials were submitted in support of this application.

7 Review of Safety

Safety Summary

No new or unexpected adverse events were seen during Study PR-00514 or Study PR-07513. Current adverse event labeling for Delzicol 400 mg delayed release tablets appears adequate and can be relied upon for the labeling of WC3079.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The swallowability study PR-00514 and relative bioavailability study PR-07513 were reviewed for safety. However, since the swallowability study PR-00514 used placebo tablets, minimal safety assessments were performed.[3] Thus, except when noted, the safety results below pertain to the relative bioavailability study (Study PR-07513).

7.1.2 Categorization of Adverse Events

Adverse events were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, Version 15.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pooling of safety data was not appropriate for this application. Each of the two trials submitted were reviewed separately.

[3] No AEs were reported during the study. No deaths or other SAEs were reported, and no subjects discontinued from the study as a result of an AE (or any other reason).

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. See Table 5 below. Subjects were to be monitored for six hours following drug administration and Investigators were to be available to be contacted by patients for the remainder of the day of study drug administration. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, and physical examination parameters. Subjects who were given at least one dose of the study medication were included in the safety analysis population. Subjects who experienced any AE were to be followed until the AE resolved, stabilized, or was no longer deemed serious enough to warrant follow-up.

Table 5. Study Flow Chart, Study PR-07513

Assessment	Screening[a]	Day -1 (Check-in Visit) All Periods[b]	Day 1 All Periods	Days 2 to 4 All Periods	Final Tests[c]
Provide subject with study information	X				
Obtain informed consent	X				
Inclusion/exclusion criteria	X				
Demographic data	X				
Medical/surgical history	X				
Height	X				
Weight	X				X
Physical examination	X				X
12-lead ECG	X				X
Vital signs[d]	X		X	X	X
Laboratory tests (hematology, serum chemistry & urinalysis)	X[e]				X
Urine pregnancy (females only)	X	X			
Serology test	X				
Check-in visit questionnaire		X			
Urine drug, cotinine, and alcohol screen	X[f]	X[g]			
Concomitant medications	X	X	X	X	X
Adverse events	X	X	X	X	X
Study medication administration			X		
PK blood sampling			X[h]		

ECG= electrocardiogram; PK = pharmacokinetic

[a] Within 28 days of Day -1 of Period 1

[b] Subjects checked into the clinic the day before each dose administration and remained in-clinic until approximately 72 hours after dosing.

[c] 'Final Tests' refers to procedures performed at approximately 72 hours postdose following the last PK blood collection of Treatment Period 5, or earlier for early withdrawals.

[d] Vital signs measurements were taken at the Screening Visit, within 2 hours prior to dosing, 72 hours postdose, and Final Tests

[e] Subjects were fasted greater than 2 hours (Screening Visit only)

[f] Urine drug and cotinine tests only; alcohol test not required at the Screening Visit

[g] Test performed on Day -1 of each dosing period; results were available prior to dosing

[h] PK blood samples were collected predose (within 2 hours prior to dosing) and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 30, 36, 48, and 72 hours postdose.

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7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

160 subjects were randomized, and 146 subjects completed all 5 treatment periods. Each subject who completed the study received 2 grams mesalamine (5 x 400 mg).

7.2.2 Explorations for Dose Response

There was no exploration for dose response.

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical data were submitted in support of this NDA.

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the submitted relative bioavailability study (PR-07513).

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see the Clinical Pharmacology Review by Dr. Sandhya Apparaju.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Patients enrolled in Study PR-07513 underwent laboratory monitoring. However, the length of the trial and number of laboratory measurements limit the ability of these tests to evaluate for possible renal, pancreatic, and hepatic adverse events—events known to be associated with mesalamines. The studies did not reveal any new safety signals.

7.3 Major Safety Results

All 160 subjects had at least one dose of study drug and were included in the safety analyses. In total, 76 subjects (48%) who received mesalamine reported at least 1 treatment-emergent AE (TEAE) (Table 6). Fifty-five (36%) of the 156 subjects who received WC3079 capsules (Test fasted), 24 (16 %) of the 148 subjects who received (Test fed) and 38 (24%) of the 157 who received Asacol tablets (Reference) reported TEAEs. The nature and frequency of TEAEs were similar for both products. The most commonly reported TEAEs were headache and nausea and were reported more frequently in subjects treated with WC3079 capsules (Test Fasted). See Table 6 below.

Table 6. Summary of Safety Results

Category	Associated Treatment			Total N=160
	WC3079 Capsule, 400 mg Fasted N=156	WC3079 Capsule, 400 mg with Food N=148	Asacol Tablet, 400 mg Fasted N=157	
TEAEs	55 (35.3%)	24 (16.2%)	38 (24.2%)	76 (47.5%)
Related TEAEs	32 (20.5%)	9 (6.1%)	21 (13.4%)	49 (30.6%)
TEAE Leading to Withdrawal	3 (1.9%)	0 (0.0%)	1 (0.6%)	4 (2.5%)
Serious TEAEs	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note:
1. This table presents the number (%) of subjects with at least one event in the respective category.
2. Related TEAEs are events reported with 'Possible' or 'Probable' relationship to study drug.

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7.3.1 Deaths

There were no deaths.

7.3.2 Nonfatal Serious Adverse Events

One patient had a serious adverse event. This was a 45-year-old, Hispanic female subject who was assigned to Sequence C (1-2-3-1-2) in the study. She received her final dose of study drug (a single mesalamine delayed release capsule, 400 mg) in the fasted state on Feb 28, 2014 and went on to complete the study. On March 5, she experienced severe epigastric pain (subsequently diagnosed as pancreatitis) that was considered by the Investigator to be treatment-related. The pain recurred on March 7, 8, and 10.

On (b) (6), she was admitted to the hospital with severe epigastric pain, bloating, nausea, and loose stools. Liver function test results were elevated, including GGT (409 U/L [normal range = 5 to 55 U/L]), as was the AST/ALT ratio, all of which were suggestive of alcohol abuse. Her white blood cell count was elevated at 15.7

The subject had a history of alcohol use in excess. At the time of admission she reported having wine the night before and a recent history of taking herbal medicine; at follow-up, she denied ever having taken herbal medicine.

The subject received IV fluids and morphine continuously throughout her hospital stay, along with ondansetron for nausea/vomiting. She was discharged from the hospital on (b) (6) with diagnoses of acute pancreatitis secondary to alcohol use and alcoholic hepatitis. At discharge, her WBC was normal. Her GGT values in the study screening visit were normal; however, the values remained above the upper limit of normal at the final/follow up visits but these were not considered by the Investigator to be clinically significant. The subject recovered from the pancreatitis with no sequelae.

7.3.3 Dropouts and/or Discontinuations

Four (3%) of the 160 subjects were discontinued from the study because of an AE. At the time of the AE, all four subjects had been treated with study drug in the fasted state. Subsequently, all subjects recovered from their adverse events with no sequelae.

- Subject 521001
  Mild lower back pain considered by the Investigator not related to study drug.

- Subject 521025
  Mild sinus congestion considered by the Investigator not related to study drug.

- Subject 521087
  Moderate headache considered by the Investigator to be related to study drug..

- Subject 521099,
  Mild nausea considered by the Investigator to be related to study drug. The

7.3.4 Significant Adverse Events

No significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission-specific safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events were headache, nausea, and arthropod bite. Each of these events (except arthropod bite) is in the current Asacol 400 mg tablets label which will be the basis for the Delzicol label. During Study PR-07513, with the exception of arthropod bite, no new or unexpected adverse events were reported. See Table 7 in Section 9.4 for a complete listing of adverse events.

7.4.2 Laboratory Findings

No clinically significant abnormal l laboratory values were identified.

7.4.3 Vital Signs

No clinically significant vital sign abnormalities were noted.

7.4.4 Electrocardiograms (ECGs)

No clinically significant ECG abnormalities were noted.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted in support of this application.

7.4.6 Immunogenicity

Not applicable. The Applicant did not provide any clinical or adverse event data regarding immunogenicity in this application.

7.5 Other Safety Explorations

No other safety explorations were performed.

7.5.1 Dose Dependency for Adverse Events

Not Applicable. All patients were treated with the same dose of both study medications.

7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted.

7.5.3 Drug-Demographic Interactions

No drug-demographic interactions were explored.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were explored.

7.5.5 Drug-Drug Interactions

The following have been identified as potential interactions based upon reports of interaction between other products containing mesalamine.

1. The concomitant use of mesalamine with known nephrotoxic agents, including nonsteroidal anti-inflammatory drugs and azathioprine may increase the risk of renal reactions.
2. In patients receiving azathioprine or 6-mercaptopurine, concurrent use of mesalamine can increase the potential for blood dyscrasias.

Study PR-07513 was not designed to allow for a review of these interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application. Results from preclinical carcinogenicity studies have been previously reviewed and are reflected in the current Delzicol 400 mg delayed release capsules label.

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction or pregnancy data were submitted. At the current time in label negotiations with the Sponsor, the Pregnancy section of the label reads as follows:

Risk Summary

(b) (4)

Data

Animal Data

Reproduction studies with mesalamine were performed during organogenesis in rats and rabbits at oral doses up to 480 mg/kg/day. There was no evidence of impaired

fertility or harm to the fetus. The 480 mg/kg/day dose of mesalamine is about 1.9 times (rat) and 3.9 times (rabbit) [redacted]

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessments of effects on growth were included in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No case of overdose has been reported during Study PR-07513.

7.7 Additional Submissions / Safety Issues

No additional safety submissions were received during the review cycle.

8 Postmarketing Experience

Table 7: Distribution Data for Delzicol delayed-release capsules

Product/Package Size	NDC Number			Distribution Information
	Labeler Code	Core Number	Sales Unit Code	Quantity
DELZICOL® (mesalamine) delayed-release capsules (Sample)	[redacted]			[redacted] capsules
DELZICOL® (mesalamine) delayed-release capsules (Trade)				[redacted] capsules

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The most recent annual report covered the period of February 01, 2014 through January 31, 2015. During this time, no supplements were submitted as a result of information pertinent to the safety. In addition, there were no safety studies completed or submitted during this reporting period.

According to the Sponsor, a review of the published literature during this period determined that there is no significant information regarding the safety, effectiveness, or labeling of the drug product.

However, due to concerns regarding the swallowability of the previously approved Delzicol 400 mg capsule (old formulation), the Sponsor was requested to prepare an update on the reports of swallowing difficulties 6-12 *months after the approval of the efficacy supplement for pediatric patients 12-17 years old),*,

This report was submitted on June 4, 2015. Eighty-four case reports related to either difficulty swallowing Delzicol DR 400 mg capsules or to the reported opening of capsules have been reported since the approval of this dosage form on February 01, 2013 until May 26, 2015[4].
There were 60 reports relating to swallowing difficulties; in at least 43% of cases (26/60) this was probably the result of the large size of capsules, due to co-reported complaints on capsule size. In the remainder of cases, patients either complained that the capsules were sticky or provided no reason for their swallowing difficulties.

Seventeen percent (10/60) of patients with reported swallowing difficulties opened the capsules in order to take their medication due to the large size of the capsule.
In addition to the 10 patients with co-reported swallowing difficulties, there were 24 additional reports of patients opening capsules without any additional explanation (in most of situations) that would suggest that the size of the capsule and difficulty swallowing would be the underlying cause.
Nevertheless, there is a potential that opening capsules was the result of swallowing difficulties, due to capsule's size.

The majority of the above cases would be considered mild to moderate in severity, with most patients experiencing only discomfort; however, while there were no fatal cases, nor any cases that were reported as serious, a single case was reported where Delzicol capsules got "sticky and stuck in [a patient's] throat, causing his esophagus to swell and close". The patient went to the emergency room, where he received a shot (not otherwise specified) and the swelling improved. This case indicates that a small but distinct potential for serious consequences secondary to swallowing difficulties exists with the use of Delzicol DR 400mg capsules.

In summary, although a signal was not identified during the clinical development of the previous formulation[5], post-marketing data provided sufficient evidence to suggest that patients may experience difficulties swallowing the size (b) (4) Delzicol 400 mg capsules.

[4] Of these 84 reports, there were only two potential pediatric cases
[5] There were no cases relating to difficulty swallowing Delzicol 400 mg capsules in the bioavailability study (PR-08210) of 251 patients.

Due to the presumed approval and subsequent marketing of the reformulated Delzicol 400 mg capsules, this potential safety concerns should no longer be an issue.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

At the current time, labeling negotiations are taking place with the Sponsor, thus the final labeling recommendations are unavailable.

9.3 Advisory Committee Meeting

No advisory committee meeting was held regarding this application.

9.4

Table 8: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Study PR-07513

System Organ Class Preferred Term	Associated Treatment WC3079 Capsule Fasted N=156	WC3079 Capsule with Food N=148	Asacol Tablet Fasted N=157	Total N=160
Number of subjects with any AE	55 (35.3%)	24 (16.2%)	38 (24.2%)	76 (47.5%)
EAR AND LABYRINTH DISORDERS	2 (1.3%)	0 (0.0%)	0 (0.0%)	2 (1.3%)
EAR PAIN	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
EXTERNAL EAR PAIN	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
EYE DISORDERS	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
VISION BLURRED	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject 521157 had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.
Source: Listing 16.2.7.1
WC3079/PR-07513/programs/production/safety/aesocpt.sas SAS 9.2 09/25/2014 8:11

System Organ Class Preferred Term	Associated Treatment WC3079 Capsule Fasted N=156	 WC3079 Capsule with Food N=148	 Asacol Tablet Fasted N=157	 Total N=160
GASTROINTESTINAL DISORDERS	23 (14.7%)	5 (3.4%)	14 (8.9%)	35 (21.9%)
ABDOMINAL DISCOMFORT	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
ABDOMINAL DISTENSION	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
ABDOMINAL PAIN	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
ABDOMINAL PAIN UPPER	1 (0.6%)	0 (0.0%)	1 (0.6%)	2 (1.3%)
ABDOMINAL TENDERNESS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
APHTHOUS STOMATITIS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
CHAPPED LIPS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
CONSTIPATION	4 (2.6%)	2 (1.4%)	1 (0.6%)	6 (3.8%)
DIARRHOEA	1 (0.6%)	1 (0.7%)	3 (1.9%)	5 (3.1%)
DRY MOUTH	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
DYSPEPSIA	1 (0.6%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
ENTERITIS	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
FLATULENCE	2 (1.3%)	0 (0.0%)	1 (0.6%)	3 (1.9%)
NAUSEA	11 (7.1%)	0 (0.0%)	7 (4.5%)	16 (10.0%)
PANCREATITIS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
REFLUX GASTRITIS	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
TOOTHACHE	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
VOMITING	4 (2.6%)	0 (0.0%)	1 (0.6%)	5 (3.1%)

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject 521157 had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.

System Organ Class Preferred Term	Associated Treatment WC3079 Capsule Fasted N=156	 WC3079 Capsule with Food N=148	 Asacol Tablet Fasted N=157	 Total N=160
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (1.3%)	2 (1.4%)	2 (1.3%)	6 (3.8%)
ASTHENIA	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
CHEST PAIN	1 (0.6%)	0 (0.0%)	1 (0.6%)	2 (1.3%)
CHILLS	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
FATIGUE	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
INFLUENZA LIKE ILLNESS	1 (0.6%)	0 (0.0%)	1 (0.6%)	2 (1.3%)
PYREXIA	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
IMMUNE SYSTEM DISORDERS	1 (0.6%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
ALLERGY TO ARTHROPOD BITE	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
ALLERGY TO ARTHROPOD STING	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
INFECTIONS AND INFESTATIONS	8 (5.1%)	2 (1.4%)	1 (0.6%)	11 (6.9%)
HORDEOLUM	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
NASOPHARYNGITIS	2 (1.3%)	0 (0.0%)	0 (0.0%)	2 (1.3%)
UPPER RESPIRATORY TRACT INFECTION	5 (3.2%)	2 (1.4%)	1 (0.6%)	8 (5.0%)

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject 521157 had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.

System Organ Class Preferred Term	Associated Treatment WC3079 Capsule Fasted N=156	 WC3079 Capsule with Food N=148	 Asacol Tablet Fasted N=157	 Total N=160
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	10 (6.4%)	1 (0.7%)	4 (2.5%)	14 (8.8%)
ARTHROPOD BITE	8 (5.1%)	0 (0.0%)	3 (1.9%)	11 (6.9%)
EAR INJURY	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
FRACTURED COCCYX	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
LIGAMENT SPRAIN	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
LIMB INJURY	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
METABOLISM AND NUTRITION DISORDERS	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
DECREASED APPETITE	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (3.2%)	0 (0.0%)	2 (1.3%)	7 (4.4%)
ARTHRALGIA	0 (0.0%)	0 (0.0%)	2 (1.3%)	2 (1.3%)
BACK PAIN	2 (1.3%)	0 (0.0%)	2 (1.3%)	4 (2.5%)
MUSCLE SPASMS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
MUSCULOSKELETAL PAIN	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
PAIN IN EXTREMITY	2 (1.3%)	0 (0.0%)	0 (0.0%)	2 (1.3%)

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject 521157 had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.

System Organ Class Preferred Term	Associated Treatment WC3079 Capsule Fasted N=156	 WC3079 Capsule with Food N=148	 Asacol Tablet Fasted N=157	 Total N=160
NERVOUS SYSTEM DISORDERS	28 (17.9%)	15 (10.1%)	19 (12.1%)	46 (28.8%)
BURNING SENSATION	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
DIZZINESS	3 (1.9%)	1 (0.7%)	0 (0.0%)	4 (2.5%)
HEADACHE	26 (16.7%)	13 (8.8%)	19 (12.1%)	43 (26.9%)
HYPOAESTHESIA	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
TENSION HEADACHE	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)
TREMOR	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
PSYCHIATRIC DISORDERS	1 (0.6%)	0 (0.0%)	1 (0.6%)	2 (1.3%)
ANXIETY	1 (0.6%)	0 (0.0%)	1 (0.6%)	2 (1.3%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
BREAST TENDERNESS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (2.6%)	3 (2.0%)	7 (4.5%)	11 (6.9%)
COUGH	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
NASAL CONGESTION	0 (0.0%)	0 (0.0%)	4 (2.5%)	4 (2.5%)
OROPHARYNGEAL PAIN	2 (1.3%)	2 (1.4%)	2 (1.3%)	3 (1.9%)
SINUS CONGESTION	2 (1.3%)	0 (0.0%)	1 (0.6%)	3 (1.9%)
UPPER RESPIRATORY TRACT CONGESTION	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject 521157 had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.
Source: Listing 16.2.7.1

System Organ Class Preferred Term	Associated Treatment WC3079 Capsule Fasted N=156	 WC3079 Capsule with Food N=148	 Asacol Tablet Fasted N=157	 Total N=160
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (2.6%)	1 (0.7%)	2 (1.3%)	7 (4.4%)
DERMATITIS CONTACT	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
ECZEMA	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
HYPERHIDROSIS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
PRURITUS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
PRURITUS GENERALISED	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)
RASH	1 (0.6%)	1 (0.7%)	0 (0.0%)	2 (1.3%)
VASCULAR DISORDERS	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
HOT FLUSH	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject 521157 had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.
Source: Listing 16.2.7.1

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/s/

MARJORIE F DANNIS
08/05/2015

ANIL K RAJPAL
08/05/2015
I concur with Dr. Dannis.