

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204412Orig1s000**

**MEDICAL REVIEW(S)**

## **Addendum #2 to Clinical Review for NDA 204,412**

**Clinical Reviewer: Aisha P. Johnson MD, MPH, MBA**

**Date: 24 January 2013**

**Subject: Section 3.3 Financial Disclosure Revisions**

Errors were made in the Financial Disclosures Section of the clinical Review of NDA 204,412. See below for the original section with corrections noted.

### **3.3 Financial Disclosures**

For ~~studies 303, 304, and 404~~ Study PR-08210, the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

There no financial disclosures provided for any of the investigators who participated in Study PR-08210.

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/s/  
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AISHA P JOHNSON  
01/24/2013

ANIL K RAJPAL  
01/24/2013

**Addendum #1 to Clinical Review for NDA 204,412**

**Clinical Reviewer: Aisha P. Johnson MD, MPH, MBA**

**Date: 22 January 2013**

**Subject: Maintenance of Remission of Ulcerative Colitis, Daily Dosing Frequency**

The reformulated product, WC3045, is the subject of NDA 204,412. A safety concern regarding the use of dibutyl phthalate (DBP) as an excipient in the formulation of Asacol<sup>®</sup> 400 mg tablets led to this reformulation in which the plasticizer dibutyl phthalate (DBP) was replaced with dibutyl sebacate. A bioavailability study and dissolution testing were used to confirm that Asacol 400 mg tablets and the newly formulated WC3045 capsules are bioequivalent. No new clinical trials were conducted as part of this NDA.

The labeling for WC3045 is based on and is a PLR conversion of the labeling for Asacol 400 mg tablets. The Asacol 400 mg tablet labeling for the maintenance of remission indication lists the dose as 1.6 g daily, **in divided doses**.

A single randomized, double-blind, placebo-controlled maintenance trial comparing two doses of Asacol with placebo was relied upon for establishing efficacy. In this trial, patients treated with Asacol 1.6 g/day were dosed four times daily. However, it was decided that the daily dosing frequency in the labeling for WC3045 will remain “in divided doses” for three main reasons:

1. The original FDA reviewer for Asacol 400 mg tablets, Dr. Robert Prizont, recommended that the maintenance daily dosing be 1.6 g daily in divided doses. Without overwhelming evidence, it was decided that we should not second-guess the daily dosing frequency rationale of the person who reviewed the clinical trials.
2. Discussions with a number of recently practicing gastroenterologists revealed that Asacol 400 mg tablets are commonly dosed 800 mg twice daily (in contrast to 400 mg four times daily). It was felt that including a different daily dosing frequency than is commonly done in practice may be confusing to prescribers given that the medication has been on the market for maintenance more than 15 years.
3. A pooled efficacy analysis of four maintenance trials comparing mesalamine to sulfasalazine was relied upon for supportive evidence of the efficacy of Asacol 400 mg tablets. In these studies, Asacol 400 mg tablets was dosed 0.8 g/day to 2.8 g/day in divided doses ranging from twice daily to four times daily. These studies provided evidence that a dosing frequency other than four times daily may be appropriate.

Given these facts, the decision was made to keep the maintenance daily dosing frequency wording “in divided doses.” To provide additional dosing information for prescribers, the decision was made to add additional information into Section 14.2 (Clinical Trials, Maintenance of Remission of Ulcerative Colitis) on the number of times per day that Asacol 400 mg tablets were

dosed per day during the studies (see bolded text below). See the recommended Dosing and Administration section for NDA 204,412 below.

## 2 DOSAGE AND ADMINISTRATION

For the treatment of mildly to moderately active ulcerative colitis, the recommended dose of TRADENAME in adults is two 400 mg capsules to be taken three times daily (total daily dose of 2.4 g), for a duration of 6 weeks.

For the maintenance of remission of ulcerative colitis, the recommended dose of TRADENAME in adults is 1.6 g daily, in divided doses.

Swallow whole, do not cut, break, or chew.

TRADENAME should be dosed at least 1 hour before a meal or 2 hours after a meal.

### 14.2 Maintenance of Remission of Ulcerative Colitis

A 6-month, randomized, double-blind, placebo-controlled, multi-center study involved 264 patients treated with mesalamine delayed-release tablets 0.8 g/day (n = 90), 1.6 g/day (n = 87), or placebo (n = 87). **In the 0.8g/day arm, patients were dosed twice daily; in the 1.6 g/day arm, patients were dosed four times daily.** The proportion of patients treated with 0.8 g/day who maintained endoscopic remission was not statistically significant compared to placebo. The proportion of patients using mesalamine delayed-release tablets 1.6 g/day who maintained endoscopic remission of ulcerative colitis was in 61 of 87 (70.1 percent) compared with 42 of 87 (48.3 percent) of placebo patients ( $p = 0.005$ ).

A pooled efficacy analysis of 4 maintenance trials compared mesalamine delayed-release tablets, at doses of 0.8 g/day to 2.8 g/day, **in divided doses ranging from twice daily to four times per day**, with sulfasalazine, at doses of 2 g/day to 4 g/day. Treatment success was seen in 59 of 98 (59 percent) patients using mesalamine delayed-release tablets and 70 of 102 (69 percent) of patients using sulfasalazine, a non-significant difference.

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AISHA P JOHNSON  
01/22/2013

ANIL K RAJPAL  
01/22/2013  
I concur with Dr. Johnson.

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204,412
Priority or Standard	Priority
Submit Date(s)	31 July 2012
Received Date(s)	31 July 2012
PDUFA Goal Date	01 February 2012
Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)/ Office of Drug Evaluation III
Reviewer Name(s)	Aisha Peterson Johnson MD, MPH, MBA
Review Completion Date	26 December 2012
Established Name	Mesalamine
(Proposed) Trade Name	unknown
Therapeutic Class	Locally acting aminosalicylate
Applicant	Warner Chilcott
Formulation(s)	Delayed release capsules, 400 mg
Dosing Regimen	Two 400 mg capsules three times daily for the treatment of mildly to moderately active ulcerative colitis 1.6 g daily, in divided doses for the maintenance of remission of ulcerative colitis
Indication(s)	Treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis
Intended Population(s)	Adults with ulcerative colitis

Template Version: [March 6, 2009](#)

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Clinical Review  
Aisha Peterson Johnson MD, MPH, MBA  
NDA 204,412  
(mesalamine)

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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 WC3045 (mesalamine) 400 mg for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis.

### **1.2 Risk Benefit Assessment**

Asacol<sup>®</sup> 400 mg tablets were approved in 1992. The successful post-marketing use of Asacol<sup>®</sup> and other oral mesalamine products have made them part of the current standard of care for the treatment of patients with ulcerative colitis (UC). A safety concern regarding the use of dibutyl phthalate (DBP) as an excipient in the formulation of Asacol<sup>®</sup> 400 mg tablets led to a reformulation. The reformulated product, WC3045, is the subject of the present application. For this reformulation, the plasticizer dibutyl phthalate (DBP) was replaced with dibutyl sebacate.

Review of the relative bioavailability study (PR-08210) submitted in support of this application confirmed that WC3045 delayed release capsules are bioequivalent to Asacol<sup>®</sup> 400 mg and WC3045. Therefore, it is expected that WC3045 delayed release capsules will be as effective and at least as Asacol<sup>®</sup> 400 mg delayed release tablets. There is also the potential for a safety advantage for WC3045 given that it does not contain DBP.

Overall, it is anticipated that the benefits of WC3045 for the induction of remission and the maintenance of remission of UC outweigh the risks of WC3045 in an appropriate patient population

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

None.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

Warner Chilcott, the Applicant, has requested a partial waiver for pediatric patients ages 0 to 4 years due to the small number of pediatric UC patients in this age group making

studies in this age cohort impossible or highly impractical. The Applicant has also requested a deferral for pediatric patients 5 to 17 years of age as the adult development program is complete (b) (4). This Application is scheduled to go before the Pediatric Research Committee (PeRC) on January 9, 2013.

To date, the Applicant has completed three pediatric UC studies:

Study 2005018

(b) (4) this open-label, randomized, 29-day parallel-group study to determine mesalamine pharmacokinetics in children and adolescents (N=33) with active UC (b) (4). Patients were stratified by age (5-8 years and 9-17 years) and randomly assigned to receive every 12 hours one of 3 doses of mesalamine (30 mg/kg/day, 60 mg/kg/day, and 90 mg/kg/day) administered as Asacol<sup>®</sup> (mesalamine) delayed-release tablets, 400 mg.

Study 2007017

(b) (4) this randomized, double-blind, parallel-group, 6-week study of 2 dose levels (low dose and high dose) of mesalamine administered as Asacol<sup>®</sup> (mesalamine) delayed-release tablets, 400 mg in pediatric subjects ages 5-17 years (N=83) with mildly to moderately active UC (b) (4). Randomization was stratified by weight (17 to <33 kg, 33 to <54 kg, and 54 to 90 kg) and by disease severity (mild and moderate). (b) (4) The pediatric formulation used for this trial was Asacol 400 mg delayed release tablets.

Study 2008085

(b) (4) this randomized, double-blind, parallel-group, 26-week study of 2 dose levels of Asacol<sup>®</sup> (mesalamine) delayed-release tablets, 400 mg consisting of a high dose and a low dose in pediatric subjects 5 to 17 years of age for the maintenance of remission of UC (b) (4). This study was terminated early due to challenges with subject enrollment.

(b) (4)

(b) (4)

The Sponsor has proposed the following clinical studies (and dates) to complete the PREA requirement:



*MO Comment: In the Pediatric Plan, the Applicant proposes to*

(b) (4)

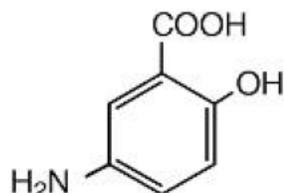


## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Trade Name:	unknown
Generic Name:	Mesalamine (5-aminosalicylic acid; 5-ASA)
Code Name:	WC3045
Chemical Name:	5-amino-2-hydroxybenzoic acid

Structural formula:



Therapeutic Class: Anti-inflammatory  
Formulation: Delayed-release capsules containing 400 mg mesalamine  
Proposed indication: Treatment of mildly to moderately active ulcerative colitis  
Maintenance of remission of 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.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Products to Treat Ulcerative Colitis

Trade Name (generic)	Induction/treatment	Maintenance
Apriso (mesalamine)		√
Asacol <sup>®</sup> 400 (mesalamine)	√	√
Asacol HD <sup>®</sup> (mesalamine)	√	
Azulfidine (sulfasalazine)	√	√
Colazal (balsalazide)		√
Dipentum (osalazine)		√
Humira	√	√
Lialda	√	√
Pentasa	√	
Remicade	√	√
Rowasa	√	
Rectal cortisone preparations	√	

## 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 204,412

Date	Regulatory Action(s)
22 April 2010	<u>Type C teleconference</u> FDA informed Warner Chilcott that as an alternative to conducting trials with clinical endpoints, it would be possible to establish bioequivalence between Asacol <sup>®</sup> 400 mg and Asacol HD <sup>®</sup> and (b) (4) reformulated products through pharmacokinetic (PK) and special dissolution studies.
02 November 2010	<u>Type C teleconference</u> The details of the PK and special dissolution studies were discussed
13 June 2012	Pre-NDA Meeting

## 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.

The Office of Scientific Investigations (OSI) performed three clinical inspections and one analytical site inspection for this application. OSI recommended that data from the inspected sites can be used in support of the NDA. See the OSI Clinical Inspection Summary for further details.

### **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**

For studies 303, 304, and 404 the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

There no financial disclosures provided for any of the investigators who participated in Study PR-08210.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

The original information provided by the Applicant was not found to be sufficient by the CMC reviewer. The final determination on whether the amended submission is sufficient to assure the identity, strength, purity, and quality of the drug product will be made after the review of information to address the deficiencies identified in CMC Review #1 (entered in DARRTS 12 December 2012 by Dr. Schroff). See the chart below for the list of CMC deficiencies communicated to the Applicant.

Table 3. CMC Deficiencies

CMC Deficiencies noted in CMC Review #1:
<p><b>1. Regarding cGMP</b> The office of compliance has not made an overall “Acceptable” recommendation</p> <p><b>2. Regarding CMC</b> The following comments should be conveyed to the applicant.</p> <p><b>Drug Substance</b></p> <ul style="list-style-type: none"><li>• Please provide specification for the drug substance, mesalamine.</li><li>• You are proposing to use two drug substance suppliers, (b) (4) (b) (4). However, all the data that you have submitted is for drug product batches manufactured with drug substance from (b) (4) (b) (4). Therefore, please withdraw the (b) (4) (b) (4) as a drug substance supplier.</li></ul> <p><b>Drug Product</b></p> <ul style="list-style-type: none"><li>• Since all core tablets for the drug product registration batches were manufactured by the “alternative process” described in Sec. 2.3.P.3.3.2.2. Please amend your application to indicate that only the “alternative process” will be used in manufacturing the commercial product, and withdraw the “original process” from the application.</li><li>• Please provide information regarding the composition of the white ink solution used to imprint the capsules. If this information can be found in a DMF, provide the DMF number, page number, and a letter of authorization from the DMF holder for FDA to review that DMF.</li><li>• Please add testing for (b) (4) to your drug product specification (release and stability).</li><li>• You have committed to (b) (4) (b) (4). Please revise that commitment to test the 180-count bottle annually (testing of the 12-count bottle is optional) and report stability failures to FDA per 21 CFR 314.81(b)(1)(ii);.</li></ul>

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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. For this reformulation, the plasticizer dibutyl phthalate was replaced with dibutyl sebacate. According to the pharmacologist/toxicology reviewer, Dr. Sruthi King, this substitution does not present any significant safety concerns for the marketing approval of WC3045.

### **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 and bioequivalence study (Study PR-08210) to confirm that the pharmacokinetic profile and bioavailability of WC3045 capsules are equivalent to Asacol<sup>®</sup> 400 mg tablets. In addition, special dissolution studies over a range of pH values were conducted to confirm that the dissolution profiles for WC3045 and Asacol<sup>®</sup> 400 mg tablets were comparable.

The clinical pharmacology reviewer, Dr. Sandhya Apparaju and the biopharmaceutics reviewer, Dr. John Z. Duan, agree that the study results confirm the bioequivalence of WC3045 and Asacol<sup>®</sup> 400 mg tablets. For further information see the full discipline reviews.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 4. Clinical Trial Submitted for NDA 204,412

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
To assess the relative bioavailability of WC3045 capsule as compared to Asacol (mesalamine) delayed-release tablet, 400 mg	Open-label, randomized, single-dose, replicate treatment, 4-period, 2-sequence, 2-formulation crossover	WC3045 capsule; single dose; oral  Asacol delayed-release tablet, 400 mg single tablet; oral	252 / 238	Healthy male and female volunteers	4 single doses

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PR-08210 is a multi-center, open-label, randomized, single-dose, replicate-treatment, 4-period, 2-sequence, 2-formulation crossover study. The study enrolled 252 healthy male and female subjects. All subjects received the following Test and Reference treatments:

- Test treatment: one mesalamine delayed release capsule, 400 mg (WC3045)
- Reference treatment: One Asacol<sup>®</sup> delayed release tablet, 400 mg

All treatments were administered orally with 240 mL of water. Treatment periods were separated by at least 7 days. Subjects were randomly assigned to one of the following 2 treatment sequences:

- Sequence A: Reference-Test-Reference-Test
- Sequence B: Test-Reference-Test-Reference

### 5.2 Review Strategy

The focus of this clinical review will be the safety results of the short-term BA/BE Study PR-08210. A recommendation for approval of WC3045 is based upon the finding that WC3045 is bioequivalent to the reference product, Asacol<sup>®</sup> 400 mg tablets. The safety results of Study PR-08210 were reviewed and no new or unexpected adverse events were seen.

### **5.3 Discussion of Individual Studies/Clinical Trials**

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. John Z. 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 relative bioavailability study, comparing the pharmacokinetic profile and bioavailability of WC3045 to Asacol<sup>®</sup> 400 mg. Study PR-08210 confirmed that WC3045 capsules have comparable PK profiles and are bioequivalent to Asacol<sup>®</sup> 400 mg tablets.

### **6.1 Indication**

Proposed indications:

- Treatment of mildly to moderately active ulcerative colitis in adults
- Maintenance of remission of ulcerative colitis

#### **6.1.1 Methods**

The Applicant submitted Study PR-08210, a relative bioavailability and bioequivalence study comparing the new mesalamine delayed release capsule 400 mg (test) to that of the approved Asacol<sup>®</sup> (mesalamine) 400 mg delayed release tablet. The study was conducted in healthy male and female subjects.

#### **6.1.2 Demographics**

Baseline demographic characteristics are summarized below in Table 5. The study enrolled 252 patients. The majority of these patients were white (80.6%) and 46.8% were female.

Table 5. Study PR-08210 Demographics

<b>Characteristic</b>	<b>Statistic</b>	<b>Result N=252</b>
Age (years)	Mean (SD)	38.5 (11.9)
	Median	37.0
	Range	18 - 60
Gender	Male	118 (46.8%)
	Female	134 (53.2%)
Race	White	203 (80.6%)
	Black	42 (16.7%)
	American Indian or Alaska native	4 (1.6%)
	Asian	1 (0.4%)
	Native Hawaiian or other Pacific Islander	1 (0.4%)
	Multiple	1 (0.4%)
Ethnicity	Hispanic/Latino	187 (74.2%)
	Non-Hispanic/Latino	65 (25.8%)
Height (cm)	Mean (SD)	165.9 (9.6)
	Median	164.0
	Range	148 - 194
Weight (kg)	Mean	71.8 (11.2)
	Median	70.2
	Range	47.6 – 110.8

Electronically copied and reproduced from Applicant's submission, Summary of Clinical Safety 2.1.2.

### 6.1.3 Subject Disposition

A total of 252 subjects were enrolled in Study PR-08210. Of those enrolled, 238 subjects completed the study. See Table 6 below for the reasons that 14 subjects discontinued the study.

Table 6. Study PR-08210 Reasons for Subject Discontinuation

<b>Reason for Discontinuation</b>	<b>Number (%) of subjects</b>
Positive drug test results	6 (2.4%)
Withdrew consent	4 (1.6%)
Adverse events	2 (0.8%)
Positive pregnancy test	1 (0.4%)
Lost to follow-up	1 (0.4%)

Reviewer's Table

#### 6.1.4 Analysis of Primary Endpoint(s)

See the Clinical pharmacology review by Dr. Sandhya Apparaju for details regarding the bioequivalence study, PR-08210.

#### 6.1.5 Analysis of Secondary Endpoints(s)

See the Clinical pharmacology review by Dr. Sandhya Apparaju for details regarding the bioequivalence study, PR-08210.

#### 6.1.6 Other Endpoints

See the Clinical pharmacology review by Dr. Sandhya Apparaju for details regarding the bioequivalence study, PR-08210.

#### 6.1.7 Subpopulations

See the Clinical pharmacology review by Dr. Sandhya Apparaju for details regarding the bioequivalence study, PR-08210.

#### 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-08210. Current adverse event labeling for Asacol<sup>®</sup> 400 mg delayed release tablets appears adequate and can be relied upon for the labeling of the bioequivalent product WC3045. In addition, given the safety concern associated with the use of dibutyl phthalate in the reference product, the new formulation (WC3045) likely offers a safety advantage for patients.

### **7.1 Methods**

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The relative bioavailability study PR-08210 was reviewed for safety. It was the only trial submitted as part of the application.

#### 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 12.1.

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

There was no pooling of data because a single study was submitted in support of this application.

### **7.2 Adequacy of Safety Assessments**

The safety assessments performed were adequate. 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 7. Study Flow Chart, Study PR-08210

Assessment	Screening <sup>a</sup>	Check-in Visit All Periods <sup>b</sup>	Day 1 All Periods	Days 2, 3 All Periods	Final tests <sup>c</sup>
Provide subject with study information	X				
Obtain informed consent	X				
Inclusion/exclusion criteria	X				
Demographic data	X				
Medical/surgical history	X				
Physical examination	X				X
12-lead ECG	X				X
Vital signs <sup>d</sup>	X		X	X	X
Laboratory tests (hematology, serum biochemistry & urinalysis)	X <sup>e</sup>				X
Serum pregnancy (females only)	X	X <sup>f</sup>			
Serology test	X				
Check-in visit questionnaire		X			
Urine drug, cotinine, and alcohol screen	X <sup>g</sup>	X <sup>f</sup>			
Concomitant medications	X	X	X	X	X
Adverse events	X	X	X	X	X
Study medication administration			X		
PK blood sampling				X <sup>h</sup>	

<sup>a</sup> Within 28 days prior to study drug administration in Period 1  
<sup>b</sup> Subjects will check into the clinic the day before each dose administration and will remain in-clinic until approximately 48 hours after dosing.  
<sup>c</sup> 'Final tests' refers to procedures to be performed at approximately 48 hours postdose following the last PK blood collection of Treatment Period 4, or earlier for early withdrawals.  
<sup>d</sup> Vital signs to be taken at Screening, within 2 hours prior to dosing, 48 hours postdose, and Final tests  
<sup>e</sup> Subjects should be fasted > 2 hours (screening only)  
<sup>f</sup> Test performed on Day -1 of each dosing period; results will be available prior to dosing  
<sup>g</sup> Urine drug and cotinine tests only; alcohol test not required at Screening  
<sup>h</sup> PK blood samples will be collected predose (within 2 hours prior to dosing) and 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 30, 36, and 48 hours postdose

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See Table 8 below for specific clinical laboratory assessments completed during the study. 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.

Table 8. Study PR-08210 Clinical Laboratory Assessments

<b>Chemistry [Fasted] (Chem-20):</b>		<b>Hematology (CBC):</b>	
Albumin	Gamma-GT	Hematocrit	(% and absolute):
Alkaline phosphatase	Glucose	Hemoglobin	Basophils
ALT	LDH	MCH	Eosinophils
AST	Phosphorus	MCHC	Lymphocytes
BUN	Potassium	MCV	Monocytes
Calcium	Sodium	Platelet count	Neutrophils
Chloride	Total bilirubin	RDW	
CO <sub>2</sub>	Total protein	RBC	
Creatinine	Uric acid	WBC	
Direct bilirubin		WBC differential	
		Reticulocyte count	
<b>Complete Urinalysis (UA):</b>		<b>Urine Screen for Drugs of Abuse:</b>	<b>Other Tests:</b>
Color and appearance		Including but not limited to the following:	HbsAg
pH and Specific Gravity		Amphetamines	HCV antibody
Bilirubin		Barbiturates	HIV antibody
Glucose		Benzodiazepines	Urine alcohol
Ketones		Cocaine (metabolite)	Urine cotinine
Leukocytes		Marijuana/Cannabinoids (THC)	Serum pregnancy (females only)
Nitrite		Methadone	
Occult blood		Methamphetamine	
Protein		Methylenedioxymethamphetamine	
Urobilinogen		Opiates	
Microscopic (including RBCs and WBCs per high powered field)		Phencyclidine	

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

Not applicable.

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-08210).

### 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-08210 underwent laboratory monitoring. However, the length of the trial and number of laboratory measurements limits 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

Treatment with WC3045 capsules was associated with adverse events in 42 (16.7%) subjects. Treatment with Asacol<sup>®</sup> 400 mg tablets was associated with adverse events in 36 (14.5%) subjects. Most adverse events reported in both groups were mild in severity. No new or unexpected adverse events were reported. There were no serious adverse events (SAEs) or deaths reported during the study.

Table 9. Summary of Safety Results

<b>Category</b>	<b>Test N=251 n (%)</b>	<b>Reference N =249 n (%)</b>	<b>Overall N=252 n (%)</b>
AEs	42 (16.7)	36 (14.5)	60 (23.8)
Serious AEs	0	0	0
AEs leading to Subject's Withdrawal	1 (0.4)	1 (0.4)	2 (0.8)
AEs Leading to Death	0	0	0
AE Severity			
Mild	32 (12.7)	26 (10.4)	49 (19.4)
Moderate	15 (6.0)	14 (5.6)	22 (8.7)
Severe	2 (0.8)	1 (0.4)	3 (1.2)
Test Treatment: one 400-mg WC3045-02 capsule Reference Treatment: one 400-mg Asacol (mesalamine) delayed-release tablet n (%) = Number (percent) of subjects who reported adverse events: (n/N)*100; nAE = number of adverse events. Subjects reporting an event in one or more treatment groups will be counted only once in the Overall column. For AE Severity, a given subject may be counted in more than one category. Source data: <a href="#">Table 14.3.1.1</a>			

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#### 7.3.1 Deaths

None.

#### 7.3.2 Nonfatal Serious Adverse Events

None.

#### 7.3.3 Dropouts and/or Discontinuations

Two subjects withdrew from the study as a result of an adverse event. Subject 506162 received a WC3045 capsule and experienced severe abdominal pain that resolved after five days. The investigator considered this event to be possibly related to the study drug. Subject 507368 received an Asacol tablet and subsequently experienced a mild rash. The investigator considered this event to be probably related to the study drug. The event resolved after 14 days.

See Section 6.1.3 for additional information regarding study dropouts.

#### 7.3.4 Significant Adverse Events

No significant adverse events were reported.

#### 7.3.5 Submission Specific Primary Safety Concerns

A review of post-marketing safety information from use of Asacol<sup>®</sup> 400 mg tablets in adults has not prompted any submission-specific safety concerns.

### **7.4 Supportive Safety Results**

#### 7.4.1 Common Adverse Events

The most common adverse events were headache, nausea, constipation, diarrhea, and abdominal pain. Each of these events is in the current Asacol<sup>®</sup> 400 mg tablets label which will be the basis for the WC3045 label. During Study PR-08210, no new or unexpected adverse events were reported.

Table 10. Common Adverse Events, Study PR-08210

MedDRA* Preferred Term Adverse Experience	Test N=251 N (%)	Reference N=249 N (%)	Overall N=252 N (%)
Any treatment-emergent AE	42 (16.7)	36 (14.5)	60 (23.8)
Headache	15 (6.0)	14 (5.6)	26 (10.3)
Nausea	8 (3.2)	6 (2.4)	13 (5.2)
Constipation	5 (2.0)	3 (1.2)	8 (3.2)
Diarrhoea	4 (1.6)	2 (0.8)	6 (2.4)
Abdominal pain	3 (1.2)	3 (1.2)	5 (2.0)
Dizziness	3 (1.2)	1 (0.4)	4 (1.6)
Presyncope	1 (0.4)	3 (1.2)	4 (1.6)
Oropharyngeal pain	2 (0.8)	1 (0.4)	3 (1.2)
Urinary tract infection	2 (0.8)	1 (0.4)	3 (1.2)
Abdominal pain upper	2 (0.8)	0	2 (0.8)
Asthenia	2 (0.8)	0	2 (0.8)
Back pain	1 (0.4)	1 (0.4)	2 (0.8)
Catheter site pain	0	2 (0.8)	2 (0.8)
Dyspepsia	1 (0.4)	1 (0.4)	2 (0.8)
Rash	1 (0.4)	1 (0.4)	2 (0.8)
Somnolence	2 (0.8)	0	2 (0.8)
Syncope	2 (0.8)	0	2 (0.8)

\*MedDRA = Medical Dictionary for Regulatory Activities version 12.1

#### 7.4.2 Laboratory Findings

Two subjects (506162 and 509644) had clinically significant abnormal urinalysis values. Both patients were diagnosed and treated for urinary tract infection. At the final study visit, all values had returned to normal.

No other clinically significant clinical 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. No new non-clinical safety studies were conducted in support of this application.

#### 7.5.1 Dose Dependency for Adverse Events

Not Applicable. All patients were treated with the same dose (400 mg) 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-08210 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 Asacol 400 mg tablets label and will be reflected in the new WC3045 label.

### **7.6.2 Human Reproduction and Pregnancy Data**

The current Asacol<sup>®</sup> 400 mg label has the drug listed as a Pregnancy Category C due to the concerns related to the presence of dibutyl phthalate (DBP) in this formulation. The proposed labeling for the WC3045 formulation lists the drug as a Pregnancy Category B. This change is appropriate given that the new formulation does not contain DBP and other mesalamine products are Pregnancy Category B.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

Asacol<sup>®</sup> 400 mg is currently indicated only for adults.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

No case of overdose has been reported during Study PR-08210.

## **7.7 Additional Submissions / Safety Issues**

No additional safety submissions were received during the review cycle.

## **8 Postmarket Experience**

The most recent annual report covered the period of 26 April 2011 to 25 April 2012. During this time, there were no unpublished clinical trials, reports, or summaries of published reports of new toxicological findings. In addition, there were no unpublished clinical trials in pediatric patients reported during the reporting period.

## 9 Appendices

### 9.1 Literature Review/References

None

### 9.2 Labeling Recommendations

The Applicant is proposing that WC3045 capsules have an indication statement that includes induction of remission and maintenance of remission of UC. These indications are identical to the indications for the Asacol<sup>®</sup> 400 mg tablets (the reference product).

The Applicant is proposing that WC3045 capsules are Pregnancy Category B consistent with other mesalamine products. In May 2010, the Pregnancy Category of Asacol<sup>®</sup> 400 mg tablets was changed from B to C due to the safety concerns associated with the use of DBP in the formulation.

*MO Comment: The proposed labeling indications appear appropriate given that they are the same indications for Asacol<sup>®</sup> 400 mg delayed release tablets. Additionally, because WC3045 capsules do not contain DBP, it is appropriate that they are Pregnancy Category B consistent with other mesalamine products.*

### 9.3 Advisory Committee Meeting

No advisory committee meeting was held regarding this application.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AISHA P JOHNSON  
12/26/2012

ANIL K RAJPAL  
12/26/2012  
I concur with Dr. Johnson.



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2  Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			x	Asacol (mesalamine) delayed-release tablets, 400 mg is an approved product. Only safety data from the bioavailability study PR-08210 was submitted.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			x	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	
25.	Have narrative summaries been submitted for all deaths and			x	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			<p>Submitted partial waiver for 0-4 year age group appears appropriate. Must submit the scientific rationale and data to support partial waiver (e.g. epidemiologic information and use data for Asacol and other mesalamine products in pediatric patients).</p> <p>Submitted deferral for the pediatric assessment. Sponsor believes that (b) (4)</p> <p style="text-align: right;">(b) (4)</p>
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			study PR-08210 adverse events dataset has been submitted
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			PR-08210 study report Section 5.2 Ethical Conduct of the Study

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes**\_\_\_\_\_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sponsor should submit:

- the scientific rationale and data to support partial waiver (e.g. epidemiologic information and use data for Asacol and other mesalamine products in pediatric patients).
- an annotated version of label with exact changes(from label of reference drug product) clearly documented

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Marjorie Dannis  
Reviewing Medical Officer

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September 10, 2012  
Date

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Clinical Team Leader

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARJORIE F DANNIS  
09/10/2012

ANIL K RAJPAL  
09/10/2012