CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 1, 2013
From	Sue-Chih Lee, Ph.D. Clinical Pharmacology Team Leader CDER/OTS/OCP/DCP3
Subject	Cross-Discipline Team Leader Review
NDA#	204412
Applicant	Warner-Chilcott
Date of Submission	Aug. 1, 2012
PDUFA Goal Date	Feb. 1, 2013 (priority review)
Proprietary Name / Established (USAN) names	Delzicol / Mesalamine
Dosage forms / Strength	Delayed-Release Capsules; 400 mg
Proposed Indication(s)	Treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis; both in adults only
Recommended Action	*Approval*

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1. Introduction

This original NDA, received on August 1, 2012, is for a new oral dosage form (capsule) of mesalamine delayed-release formulation at a 400-mg strength. The Applicant currently has mesalamine delayed-release tablets (Asacol) 400 mg on the market. Due to the safety concern about dibutyl phthalate (DBP) in the enteric coating of Asacol tablets, the Applicant developed this new formulation that does not contain any phthalate. The proposed indications and dosing regimens are exactly the same as those for Asacol tablets, i.e., it is for the treatment of mildly to moderately active ulcerative colitis (800 mg TID) and for the

maintenance of remission of ulcerative colitis (1.6 g daily, in divided doses), both for adults only. No safety and efficacy trials were conducted by the Applicant using the proposed capsule product. To support the proposed product, the Applicant conducted a comparative PK study and comparative dissolution studies to establish bioequivalence of the proposed product to the reference product, Asacol Tablets 400mg.

Since this 505(b)(1) NDA was submitted to address a safety concern, the Application received a priority review status with a 6-month review clock. The Applicant intends to withdraw Asacol Tablets 400 mg from the market once the current NDA is approved.

2. Background

The mechanism of action of mesalamine for the treatment of ulcerative colitis is unknown, but mesalamine appears to have a topical anti-inflammatory effect on the colonic epithelial cells. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease. It is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting postaglandin production in the colon.

2.1 Regulatory History

2.1.1 Approved Mesalamine Drug Products for Ulcerative Colitis

Several approved mesalamine products are currently on the market for the treatment of mildly to moderately active ulcerative colitis and/or maintenance of remission of ulcerative colitis (Table 1). There are also mesalamine prodrugs available such as Azulfidine (sulfasalazine), Colazal (balsalazide) and Dipentum (osalazine). Additionally, several corticosteroid products are also available for mildly to moderately active ulcerative colitis, including the recently approved Uceris extended-release tablets. Of the mesalamine products listed in Table 1, Asacol HD also contains DBP (b) (4)

Table 1. Approved mesalamine products for ulcerative colitis currently on the market

Trade Name ***Dosage form, approval year***	***Induction***	***Maintenance***
Apriso Extended-release capsules, 2008	-	1.5 g/day (QD)
Asacol HD® Delayed-release tablets, 2008	4.8 g/day – moderately active UC (TID)	-
Lialda Delayed-release tablets, 2007	2.4 – 4.8 g/day (QD)	2.4 g/day (QD)
Pentasa Extended-release capsules, 1993	4g/day (QID)	-
Asacol® 400 Delayed-release tablets, 1992	2.4 g/day (TID)	1.6 g/day (in divided doses)
Rowasa Rectal Suspension Enema, 1987	4g (QD)	-

2.1.2 Regulatory History of the Proposed Product

Asacol (mesalamine delayed-release tablets 400 mg; NDA 19-651) contains a plasticizer dibutyl phthalate (DBP), which has been linked with harmful effects on fetus in animal studies at high doses. The Applicant was advised of reformulating the product to eliminate DBP. Subsequently, the Applicant developed a new formulation that uses dibutyl sebacate to replace DBP as the plasticizer in the enteric coating. The proposed formulation is an over-encapsulated tablet and contains the same release-controlling excipient, Eudragit S, as the approved Asacol tablets 400 mg.

During the course of the reformulation, several events occurred as summarized below in chronological order:

- A Type C teleconference was held on April 22, 2010, during which the Agency informed the Applicant that, as an alternative to conducting trials with clinical endpoints as previously recommended for locally acting mesalamine products, it would be possible to establish bioequivalence between two mesalamine delayed-release formulations through pharmacokinetic (PK) and special dissolution studies.

- In the response* dated August 20, 2010, to two Citizen Petitions (FDA-2010-P-0111 and FDA-2008-P-0507), the Agency indicated that comparative PK studies should be used in lieu of comparative clinical trials to assess bioequivalence for mesalamine modified-release products along with dissolution testing. For PK studies, however, the standard PK metrics will not be sufficient and other metrics obtained by analyzing PK profiles over a defined time interval (e.g., partial AUC, mean residence time and steady state Cmax) will be necessary in lieu of or in addition to standard metrics. In addition, the replicate design with reference-scaled BE analysis methodology is suitable for highly variable drugs such as mesalamine.

  *Reference: US Food and Drug Administration. Response to Citizen Petitions (Docket Nos. FDA 2010-P-0111 and FDA-2008-P-0507) <http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0111-0011>

- At a Type C meeting held on November 2, 2010, the details of the PK and dissolution requirements were discussed further. During this meeting, the agency agreed with the sponsor to include a partial AUC in addition to the traditional PK parameters (Cmax and AUC) to ensure profile similarity as part of a bioequivalence approach that also includes assessment of similarity of dissolution profiles at various median pH's. The Agency recommended characterizing the latter portion of the PK profile for partial AUC and agreed that a reference-scaled average BE approach for highly variable drugs would be appropriate. However, there was no agreement on a specific time interval for the partial AUC.

- At the above mentioned Type C meeting held on November 2, 2010, the agreement for dissolution testing was as follows:

Apparatus:	USP Apparatus 2 (paddle)
Pretreatment Stage:	2 hours in 0.1 N HCl at 100 rpm

Evaluation Stage: Each of
(1) pH 4.5 Acetate buffer at 50 rpm
(2) pH 6.0 Phosphate buffer at 50 rpm
(3) pH 6.5 Phosphate buffer at 50 rpm
(4) pH 6.8 Phosphate buffer at 50 rpm
(5) pH 7.2 Phosphate buffer at 50 rpm
(6) pH 7.5 Phosphate buffer at 50 rpm
Volume: 900 mL
Temperature: 37ºC
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150 minutes or as needed
At least 12 tablets from each lot (test and reference) should be used per test.
The f2 metric should be used to compare dissolution profiles.

- In the advice letters dated February 15, 2011 and December 5, 2011 following separate reviews of the Applicant's proposed and revised study protocols, respectively, the Agency recommended a full replicate study design (i.e. both test and reference products administered twice), and recommended statistical analyses of three metrics (Cmax, AUC0-tldc, AUC8-48h) in the proposed study that compared the PK between the proposed formulation and Asacol tablets. The Agency recommended the partial AUC8-48h as opposed to the (b) (5) proposed by the sponsor since the time period 8-48 hours was considered by the Agency to be more clinically relevant and was expected to be able to detect significant differences in product performance. The Agency also noted that additional exploratory parameters, such as (b) (4) (0-12 and 12-48 hours, etc.) may be included as secondary endpoints.

- At the pre-NDA meeting held on June 13, 2012, the Agency reiterated that a comparative clinical endpoint study will not be required if bioequivalence based on PK metrics and dissolution comparability have been established. The Agency also clarified that a reference-scaled average BE approach for highly variable drugs can be employed even when the intra-subject variability exceeds 100%.

2.2 Current Submission

In this NDA, the Applicant provided an in vivo bioequivalence (BE) study using Asacol tablets as the reference product, in vitro comparative dissolution testing results, and in vitro alcohol dose dumping studies. There are special features in these studies: (1) Since oral mesalamine delayed release formulations are considered locally acting, both the BE study and dissolution testing differ from the standard studies for systemic drugs, and (2) Because Asacol tablets exhibit high intrasubject variability, the reference-scaled average BE methodology is used in lieu of the standard two one-sided t-tests. Note that reviews of many disciplines refer to the proposed capsule formulation as WC3045 capsules.

2.3 NDA Review Documents

All the relevant review disciplines have written review documents as listed below. The review document dates cited here refer to dates of final signoff in DARRTS.

- Clinical Pharmacology Reviews by Sandhya Apparaju, dated December 20, 2012 and January 11, 2013
- Clinical Review by Aisha Johnson, dated December 26, 2012
- PMHS review (re: maternal health) by Jeanine Best, dated January 11, 2013
- PMHS review (re: PREA requirements) by Erica Radden, dated January 30, 2013
- Pharm/Tox review by Sruthi King, dated December 20, 2013
- ONDQA Biopharm reviews by John Duan, dated December 28, 2012 and January 12, 2013
- CMC Reviews by Hitesh Shroff, dated December 12, 2012 and February 1, 2013
- OSI Report by Sripal Mada, dated January 8, 2013
- DMEPA labeling review by Denise Baugh, dated January 9, 2013
- DMEPA proprietary name acceptance letter by Carol Holquist, dated January 25, 2013
- OPDP Labeling Review by Kathleen Klemm, dated January 16, 2013

3. ONDQA Reviews - CMC and Biopharm

(A) CMC REVIEW

The reader is referred to the Drug Product and Drug Substance Reviews by Dr. Hitesh Shroff dated December 12, 2012, and February 1, 2013 for complete information.

The formulation for the proposed capsules and the approved Asacol tablets are shown in Table 2. Each proposed capsule contains a tablet that has a similar formulation as the Asacol tablet except that the proposed formulation has dibutyl sebacate to replace DBP.

Table 2. Components and Composition of the proposed capsules vs. Asacol tablets

Ingredient	Unit Quantity (mg/dosage form)	
	WC3045 Capsules Formulation WC3045-02 (Material Number (b) (4) (b) (4)	Asacol (mesalamine) Delayed-release Tablets, 400 mg
5-Aminosalicylic acid (5-ASA, mesalamine), USP	400.0	400.0
Lactose Monohydrate, NF	(b) (4)	
Povidone, USP		
Sodium Starch Glycolate, NF		
Magnesium Stearate, NF		
Talc, USP		
Colloidal Silicon Dioxide, NF		
Subtotal		
Methacrylic acid copolymer, NF, type B (Eudragit S (b) (4)		
Talc, USP		
Dibutyl sebacate, NF		
Dibutyl phthalate, NF		
Ferric oxide, NF, red		
Ferric oxide, NF, yellow		
Subtotal		
Polyethylene glycol (b) (4)		
Subtotal		
HPMC capsule printed with white ink (b) (4) Clear Print)		
TOTAL		

[1] Eudragit S (b) (4) s an isopropyl alcohol solution containing (b) (4) methacrylic acid copolymer, NF Type B

There were several deficiencies related to drug substance and drug product following an initial review by Dr. Hitesh Shroff and all these CMC deficiencies were communicated to the Applicant on December 7, 2012 . The Applicant subsequently submitted their responses to address these deficiencies and Dr. Shroff found the responses acceptable. In addition, the Office of Compliance made a final overall "Acceptable" recommendation on February 1, 2013, for the cGMP related to this NDA.

CMC issues identified in Dr. Shroff's review dated December 12, 2013 and the subsequent resolution:

Regarding drug Substance: The Applicant has been requested to do the following:

- Provide specification for the drug substance, mesalamine.
- Withdraw the (b) (4) as a drug substance supplier.

Dr. Shroff's comments in the 2/1/13 review: The Applicant provided the specification for mesalamine and withdrew the (b) (4) *as a drug substance supplier.*

Regarding drug product, the following information requests were made on December 7, 2012:

- 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.

  Dr. Shroff's comments in the 2/1/13 review:
  The Applicant has provided sufficient evidence to demonstrate that both original and alternative manufacturing process can produce comparable drug product that meet the specification. Thus, both original and alternative core tablet manufacturing methods will be acceptable.

  The Applicant also provided information to address the following three deficiencies, which were found to be acceptable.

- 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.
- Please add testing fo (b) (4) to your drug product specification (release and stability).
- You have committed to (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).

(B) ONDQA BIOPHARM REVIEW

The reader is referred to the reviews by Dr. John Duan dated December 28, 2012 and January 12, 2013, for complete information.

Dissolution Testing:

The Applicant conducted dissolution testing using dissolution media of various pH values (i.e., 0.1N HCl, and buffer solutions at pH 4.5, 6.0, 6.5, 6.8, 7.2 and 7.5) and performed multipoint dissolution profile comparisons between the proposed capsule formulation and Asacol delayed-release tablets 400 mg as recommended by the Agency in the Type C teleconference with the Applicant, held on November 2, 2010. The similarity factors (f2) values were calculated and provided.

However, the variability is high for either the reference or the test product. In principle, the f2 does not apply when the CV is more than 20% at early time point or more than 10% at

later time point. Therefore, Dr. Duan performed bootstrapping to evaluate f2. Twelve (12) dosage units were randomly selected with replacement for reference and test product. The means of these selected units at each time point were obtained and used for f2 calculation. The process was repeated for 10,000 times. The bootstrap mean represents the average over the 10,000 sample means. The distribution of the calculated f2 values was obtained and the 90% confidence intervals were calculated using percentile and bias-corrected and accelerated (BCA) approaches. The 90% lower limits of BCA bootstrapped f2 are 50 or more in all the dissolution media tested. As such, the analysis established similarity between the test and reference products.

Further, the proposed dissolution specification acceptance criterion at Stage 3 (pH 7.2), Q=80% at 1.5 hrs (using Type II Paddle 50 RPM) is not optimal. An acceptance criterion of Q=80% at 75 minutes seems more appropriate based on the data available. Since limited data at 75 minutes are available, additional data will need to be collected post-approval. The Applicant has committed to do so and to submit a supplement to finalize the specification. (See Section 12.6 for more information on the PMC.) At this time, the Applicant's proposed dissolution acceptance criteria as listed below are accepted as interim criteria:

Interim dissolution acceptance criteria:

- 0.1N HCl (Type II Paddle 100 RPM, 2 hrs): No individual value exceeds 1% dissolved
- pH 6.0 (Type II Paddle 100 RPM, 1 hr): No individual value exceeds 1% dissolved
- pH 7.2 (Type II Paddle 50 RPM): Q=80% at 1.5 hrs

To-be-marketed formulation vs. the clinical formulation:

The clinical batch (Material Number 33075301) and to-be-marketed batch (Material Number 40000024) have the same unit-dose composition and manufacturing process for the core tablets and coating process. The following three differences are noted: (1) change capsule shell size from size (b) (4) to size (b) (4) (2) change capsule shell/ink color from (b) (4) (b) (4) (3) change encapsulation process from (b) (4)
The changes between the clinical and the to-be-marketed fo
correspond to Level 1 changes. The dissolution profiles of the clinical and the to-be-marketed formulations were characterized using the proposed dissolution test method and the dissolution metric f2 showed that dissolution profiles were similar. Bootstrapping was not conducted because the mean dissolution profiles were almost overlapping with each other between the clinical and the to-be-marketed formulations. Therefore, these two formulations are expected to have similar *in vivo* performance.

In vitro alcohol dose dumping studies:

As noted in Dr. Duan's review, there is no significant risk of alcohol dose dumping with the proposed formulation. His review has the following comments:

Although the delayed release characteristics are maintained in Phase 1 - 0.1N HCl and Phase 2 –pH 6 when the media contain up to 40% alcohol in the acid stage (Phase I), the profile at Stage 3 (pH 7.2) was affected significantly when the alcohol concentration reached 20% and above. It is also noted that alcohol was only added to the acid stage (Stage 1). At Stage 2 (pH 6.0) and Stage 3 (pH 7.2), no alcohol was present. Because the highest concentrations of

alcohol in GI tract are likely to be encountered in the acidic environment of the stomach, the dissolution profiles generated in 0.1 N HCl with different concentrations of alcohol are more clinically relevant (as compared to dissolution profiles generated in dissolution media at other pH's, containing alcohol). Therefore, we consider the study addressed the alcohol induced dose dumping potential. A faster dissolution was shown at pH 7.2 medium when the alcohol concentrations reached 20% or more. However, the delayed release characteristics had not been compromised because the dissolution in Phase 1 - 0.1N HCl and Phase 2 –pH 6 was zero and the formulation has been designed to release the drug at pH 7. The faster dissolution at pH 7.2 in the presence of high concentration (≥20%) of alcohol may not raise a safety concern.

3.1 Final Recommendation

This NDA is recommended for approval from a CMC perspective. The issues with drug substance and drug product have been resolved and the Office of Compliance made an overall "Acceptable" recommendation on February 1, 2013. (The Applicant's proposed dissolution acceptance criteria are considered interim criteria, which need to be finalized post-approval, i.e., not an approval issue. A PMC is listed in Section 12.6.)

4. Nonclinical Pharmacology/Toxicology

The reader is referred to the review by Dr. Sruthi King dated December 20, 2012 for complete information.

No new nonclinical pharmacology/toxicology information is provided by the Applicant to support this application. However, the Nonclinical Pharmacology/Toxicology Review has several labeling comments. Notably, a pregnancy category B is recommended now that the proposed formulation does not contain DBP. The plasticizer used in the proposed formulation is dibutyl sebacate, which is listed in the FDA Inactive Ingredient Database and has been previously used at higher amounts in FDA-approved oral formulations. Dr. King noted no significant safety concerns for the marketing approval of the proposed product. (Note that DBP is an inactive ingredient in Asacol's enteric coating, and in animal studies at doses >190 times the human dose based on body surface area, maternal DBP was associated with external and skeletal malformations and adverse effects on the male reproductive system. In May 2010, the Pregnancy Category of Asacol® 400 mg tablets was changed form B to C due to the safety concerns associated with DBP in the formulation.)

Besides change in pregnancy category, another significant change in the labeling is to add a section (Section 13.2) on Animal Toxicology and/or Pharmacology to the label. This section is to include toxicities observed from studies in rats, mice and dogs, which were reviewed previously. There are also recommendations on addition of subheadings to add readability.

4.1 Final Recommendation

An "Approval" action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline.

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the reviews by Dr. Sandhya Apparaju dated December 20, 2012 and January 11, 2013 for complete information.

To support the proposed capsule formulation, the Applicant conducted a study entitled "A Study to Assess the Relative Bioavailability of Two WC3045 Formulations in Healthy Subjects, Study PR-08210." The study demonstrates that the proposed capsule formulation is bioequivalent to the reference product (Asacol Tablets) under the conditions studied (fasting).

Study PR-08210 was an open-label, randomized, single-dose, replicate treatment, 4-period, 2-sequence, 2-formulation crossover study comparing the proposed formulation 400 mg to the reference product Asacol Tablets 400 mg. All treatments were administered orally with 240 mL of water under fasting conditions. 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

The metrics for comparison included Cmax, AUC0-tldc and AUC8-48h. The partial AUC (AUC8-48h) was recommended by the Agency as it was considered to reflect drug absorption (and therefore drug availability) at the site of action in the colon. The reference-scaled average BE approach for highly variable drugs (i.e., intrasubject standard deviation for the reference product, $S_{WR} \geq 0.294$) was used to analyze the data. The study design, PK metrics and data analysis methodology were agreed upon between the Agency and Applicant during the formulation development. With this data analysis methodology, the BE acceptance criteria (Reference: OGD Draft Guidance on Progesterone) for all three PK metrics are:

(1) Geometric mean ratio (T/R): $0.8 \leq T/R \leq 1.25$

and

(2) 95% upper confidence bound of $\left(\bar{Y}_T - \bar{Y}_R\right)^2 - \theta s^2_{WR} < 0$

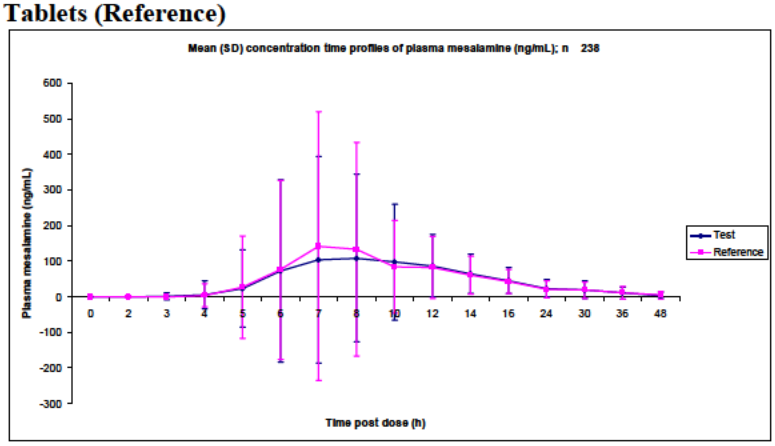
Where:

- $\bar{Y}_T$ and $\bar{Y}_R$ are the means of the ln-transformed PK endpoint (. obtained from the BE study for the test and reference products
- $\theta \equiv \left(\frac{\ln(1.25)}{\sigma_{W0}}\right)^2$ (scaled average BE limit)
- and $\sigma_{W0} = 0.25$ (regulatory limit)

Study results:

Study PR08210 enrolled 252 subjects and 238 completed the study. Mean plasma concentration-time profiles for the test and reference mesalamine formulations are shown in Figure 1.

Fig. 1: Mean plasma mesalamine concentration-time profiles for the proposed product (Test) and Asacol Tablets (Reference)



Applicant's analysis: The Applicant's analysis results of the primary PK endpoints using the reference-scaled average BE methodology are shown in Table 3, which indicates that the proposed product passed the BE criteria for all three PK parameters. The Applicant also conducted analysis on other partial AUCs (AUC10-48h, and AUC12-48h) and both also passed the BE criteria (results not shown).

Table 3: Applicant's BE analysis results

Parameter	Geometric Mean		Within-Subject Standard Deviation		Ratio (Test /Reference)	95% upper confidence bound of the linearized criterion
	Test	Reference	Test	Reference		
Cmax	109.9	99.4	1.167	1.275	1.106	-1.105
AUC8–48	618.3	556.4	1.453	1.490	1.111	-1.514
AUC0–tldc	719.6	648.4	1.464	1.536	1.110	-1.608

Cmax = Maximum plasma concentration (ng/mL); AUC8-48 = Area under the plasma concentration versus time curve from time 8 hours to 48 hours (ng·h/mL); AUC0–tldc = Area under the plasma concentration versus time curve from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)

Agency's analysis: Dr. Sandhya Apparaju's analyses using the reference-scaled average BE methodology indicated that the proposed capsule formulation is bioequivalent to Asacol Tablets (Table 4). This is the first time BE data for mesalamine delayed-release formulations were analyzed using a partial AUC as one of the BE metrics. In addition, the mean concentrations for the test and reference products differ at hours 7 and 8. Therefore, analyses were also performed on other partial AUCs (Table 4) to better understand the data at hand. Overall, the partial AUC 8-48h appears to be a reasonable PK metric to be included for BE determination based on the analyses and physiological considerations, and the Applicant's

conclusion of bioequivalence is affirmed. It is noted that the intrasubject variability (%CV) is much greater than 100% for all three metrics (Table 5) for both the proposed product (Test) and the reference product (Asacol Tablets).

Table 4: Agency's BE analysis results

Parameter	(1) T/R Ratio	Lower 90% CI	Upper 90% CI	$(S_{WR})^2$	S_{WR}	(2) Criteria Bound	Method Used	OUTCOME
Primary Statistical Endpoints								
Cmax	1.11	95.12	122.49	1.5156088	1.2311006	-1.030364	Scaled/PE	PASS
AUC_{TLDC}	1.08	90.52	121.76	1.8493626	1.3599127	-1.265287	Scaled/PE	PASS
AUC8-48	1.10	92.89	125.92	2.0725896	1.4396491	-1.41748	Scaled/PE	PASS
Additional Analyses								
AUC6-48	1.10	92.38	126.11	2.1815445	1.4770052	-1.493384	Scaled/PE	PASS
AUC10-48	1.12	94.38	126.79	1.9880089	1.4099677	-1.355735	Scaled/PE	PASS
AUC12-48	1.10	93.90	126.05	1.9860953	1.4092889	-1.35789	Scaled/PE	PASS

S_{WR}: within-subject standard deviation (values cited in this table are for the reference product.)

Table 5: Intersubject and intrasubject variability (%CV) for Test and Reference products

	Test (WC3045 Capsules)		Reference (Asacol 400 mg tablets)	
	Inter-Subject % CV	Intra-Subject % CV	Inter-subject CV	Intra-subject CV
Cmax	148 %	170 %	165 %	200 %
AUC0-tldc	81 %	272 %	87 %	306 %
$AUC_{8\text{-}48h}$	70 %	268 %	71 %	286 %
Within-subject CV = [SQRT(EXP(sWR^2)-1)]; sWR is within-subject standard deviation from SAS output				

OSI inspection:

Because the in vivo BE study is the pivotal clinical trial to support the safety and efficacy of the proposed formulation, an OSI inspection of the following clinical and analytical sites was requested.

Clinical sites:

- Comprehensive Clinical Development, Fort Myers, FL
  - Inspections by Ethan P. Stegman/ORA on Oct. 6-9, 2012; acceptable
- Comprehensive Clinical Development, Miramar, FL.

- Inspections by Ethan P. Stegman/ORA on Oct. 22-26, 2012; acceptable

- Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX (WCTEPS)
  - Inspections by Todd R. Lorenz/ORA on Nov. 13, 2012; *Form FDA-483 issued*.

Analytical site:

- (b) (4)
  - Inspected by (b) (4) on Form FDA-483 was issued

Although Form 483 was issued for one clinical site and the analytical site following OSI inspections, the Clinical Pharmacology review dated January 12 has found the study data acceptable as the deviations did not have significant impact on the final results. Section 10.1 contains more detailed information on the inspection issues.

Comments:

1. Demonstration of bioequivalence includes two components: the in vivo BE study and in vitro dissolution testing at various pH conditions. ONDQA Biopharmaceutics Division reviewed the in vitro studies and found the studies acceptable as noted in Section 3 although the dissolution acceptance criteria require further evaluation post-approval. It should be noted that this issue with the dissolution specification does not negate the conclusion that the proposed product is bioequivalent to Asacol tablets.

2. *Label implications:* Due to the absence of food-effect information in the NDA for the proposed delayed-release capsule formulation, labeling will reflect that the drug should be administered under relatively fasted conditions (e.g. 1 h before a meal or 2 h after a meal for this TID administered drug). Label may be revised when food-effect information becomes available. Note that Asacol can be taken with or without food.

5.1 Final Recommendation

This NDA is recommended for "Approval" from a clinical pharmacology perspective.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because the proposed product is not an antimicrobial agent.

7. Clinical – Efficacy and Safety

The reader is referred to the review by Dr. Aisha Johnson dated December 26, 2012 for complete information.

7.1 Overview

No new clinical trials were conducted to demonstrate the safety or efficacy of the proposed product. Rather, clinical efficacy and safety in regard to mesalamine are inferred by establishing bioequivalence of the proposed product to the reference product, Asacol tablets 400 mg. There is the potential for a safety advantage for the proposed product given that it does not contain DBP. Overall, it is anticipated that the benefits of the proposed product for the induction of remission and the maintenance of remission of UC outweigh the risks of the product in an appropriate adult patient population.

7.2 Review Summary - Efficacy

No new clinical efficacy trials were submitted in support of this application. Efficacy of the proposed product is inferred by demonstrating bioequivalence between the proposed product and the referenced Asacol Tablets.

7.3 Review Summary - Safety

A review of safety data from Study PR-08210 revealed no new or unexpected adverse events. Current adverse event labeling for Asacol® 400 mg delayed release tablets appears adequate and can be relied upon for the labeling of the proposed product, which is bioequivalent to Asacol. In addition, given the safety concern associated with the use of DBP in the reference product, the proposed formulation likely offers a safety advantage for patients.

7.3 Final Recommendation

An "Approval" Action is recommended by the Clinical Review Team.

8. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

9. Pediatrics

The following is adapted from the review by Dr. Aisha Johnson dated December 26, 2012.

No pediatric studies were conducted using the proposed formulations. (b) (4)

(b) (4)

Study 2005018:
This was an 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® (mesalamine) delayed-release tablets, 400 mg.

Study 2007017:
This was a randomized, double-blind, parallel-group, 6-week study of 2 dose levels (low dose and high dose) of mesalamine administered as Asacol® (mesalamine) delayed-release tablets, 400 mg in pediatric patients aged 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
This was a randomized, double-blind, parallel-group, 26-week study of 2 dose levels of Asacol® (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 patient enrollment.

10. Other Relevant Regulatory Issues

10.1 Office of Scientific Investigations (OSI) audits

The reader is referred to the review by Dr. Aripal Mada dated January 8, 2013, and that by Dr. Sandhya Apparaju dated January 11, 2013, for complete information. The overall conclusion is that the bioequivalence data are acceptable for review.

An OSI inspection was requested to inspect three clinical sites and one analytical site of the pivotal bioequivalence study entitled "A Study to Assess the Relative Bioavailability of Two WC3045 Formulations in Healthy Subjects, Study PR-08210." Although the OSI inspections resulted in issuing of FDA-Form 483s (Voluntary Action Indicated, VAI) for one clinical site (Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX

(WCTEPS) and the analytical site (b) (4) it was concluded that these deficiencies did not have a significant impact on the BE study outcome.

Inspection findings:
There were one issue related to the clinical site and five issues related to the bioanalytical site as identified in FDA-Form 483s following inspections. Subsequent to Applicant's responses to these deficiencies, OSI concluded that four of these issues were adequately resolved. For the two remaining issues, OSI recommended that the Office of Clinical Pharmacology review team review the issues to make conclusions regarding data acceptability. These are detailed below:

One issue is related to the lack of documentation of timing for blood sample storage in freezer at the clinical site with a total of six samples involved in the citation. The Clinical Pharmacology review noted that 5 of the six samples had values below the limit of quantitation (BLQ) and were supported by similar BLQ findings in samples before or after this time point. In one sample, where detectable drug levels were noted, the concentration-time profile in that individual did not signal anything out of ordinary with the inclusion of data from the indicated sample. As such, the impact of these deviations is negligible.

Another issue is related to failure to apply to all samples in the respective runs the changed chromatographic integration parameters in 2 samples in runs #54 and 74. In run 54 (b) (4) #6335 was reintegrated to correct the baseline, but remained BLQ regardless of the reintegration, so there is no impact to the reported results. However, even if the new parameters applied to #6335 had been applied to the entire run, reported sample results would have changed by less than 4%. In run 74 (b) (4) #8498 was reintegrated to correct the baseline, and if these parameters are applied to the entire run sample results would have changed by less than 2%. Each of the two analytical runs (#54 and #74) noted in this issue had approximately 130 samples, along with duplicates of QCs and standards within each run. The Clinical Pharmacology review finds the impact of reintegration on the final mesalamine concentrations in runs 54 and 74 to be minimal, with the majority of samples either remaining unaffected (61 -71 % in the two runs) or minimally affected (<2 - 4 % change) upon application of reintegration.

Therefore, no further action is needed in this regard and the NDA data can be accepted without the need of further analyses of the BE data.

10.2 QT Prolongation Potential

The QT prolongation potential has not been formally studied for any mesalamine products.

11. Labeling

11.1 Proprietary name

The Division of Medication Error Prevention and Analysis (DMEPA) has reviewed several proposed proprietary names (i.e., (b) (4)) and found them unacceptable. The Applicant formally submitted the proposed name Delzicol on January 18, 2013, which was accepted by DMEPA on January 25, 2013.

In the case of the proprietary name (b) (4), which was submitted on December 14, 2012, the name was found unacceptable as communicated to the Applicant on 1/17/13 by Lubna Merchant, Team Leader, DMEPA, and Phong Do, Pharm.D., SRPM.) because of the following reasons:

(b) (4)

(b) (4)

Therefore, the proposed proprietary name implies a unique representation over other drugs with the same active ingredient, suggesting that the drug is a new form of mesalamine associated with a better efficacy profile. Given that the active ingredient is a common substance, this suggestion is misleading.

11.2 Division of Professional Drug Promotion (DPDP/OPDP) Comments

Kathleen Klemm, Regulatory Review Officer in Division of Professional Drug Promotion (DPDP), Office of Prescription Drug Promotion (OPDP) reviewed the PI. For complete information, please refer to her review dated January 16, 2013.

Her comments on the PI are as follows:

1. *Warnings and Precautions in the Highlight section:*
   Although this section is consistent with the Highlights of Asacol HD (label approved 05/24/10), the Highlights of Lialda (label approved 07/14/11) includes additional risk information in this section. Specifically, Lialda includes the following (in pertinent part):
   "Mesalamine-induced acute intolerance syndrome has been reported. Observe patients closely for worsening of these symptoms while on treatment.
   •Use caution when treating patients who are hypersensitive to sulfasalazine.
   •Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported.
   •Hepatic failure has been reported in patients with pre-existing liver disease…

   Please consider if this additional risk information should be included, for consistency and to avoid minimizing risks. If additional risk information is added, we recommend presenting it in an order consistent with the Warnings and Precautions section of the Full Prescribing Information (FPI).

2. Under section 17 PATIENT COUNSELING INFORMATION
   OPDP recommends removal of the statement (b) (4) as it implies a guarantee of efficacy.

11.3 Physician Labeling / Medication Guide / Carton and Container Labeling

DMEPA

For DMEPA comments, the reader is referred to the review by Dr. Denise Baugh dated January 9, 2013, for complete information.

DMEPA searched the FAERS database for medication errors of Asacol. There were a total of 15 cases, with 8 cases involving wrong drugs due to orthographic or phonetic similarity. Since the proposed formulation will have a different proprietary name, this factor does not appear to be relevant to the new product. The following medication errors deserve attention for improving the labeling of the proposed product:

1. *Physician labeling:* With regard to 7 cases of wrong dose or dosing frequency, DMEPA noted that the Asacol label indicated that maintenance dose is 1.6g/day in divided doses. This is considered not clear and stating a specific dosing regimen will help to clarify. The review team considered this. However, it is not clear how one can provide a specific dosing regimen when the dosing information in the original clinical trials for Asacol cannot be located.

2. *Container labeling:* There were three cases of wrong technique (e.g., chewing and cutting) despite the statements in the label and on the side panel of the container label to indicate that the dosage form should be swallow whole without cutting, breaking or chewing. Relocating this statement from the side panel to the principal display panel of the container may increase the prominence of the statement.

3. Container labeling: In addition to the above comments based on FAERS search for medication errors, the following observations by DMEPA were also noted:
    - There are several comments about readability related to line thickness of the font or spacing.
    - One comment about adding dosing message on to the container label: "Take each dose at least one hour before or 2 hours after a meal".
    - Ensure that the "New formulation" alert is implemented only for the first six months of new product marketing.

PMHS-MHT:

For PMHS-MHT comments, the reader is referred to the review by Dr. Jeanine Best dated January 11, 2013, for complete information.

Pregnancy category and Nursing mothers: PMHS-MHT commented that the proposed label regarding use in pregnant and lactating women is appropriate. A pregnancy category B is the appropriate pregnancy category classification for this product because animal data as well as limited human data failed to show evidence of fetal harm and that DBP has been removed from the product. They recommend re-structuring of the pregnancy and nursing mothers

labeling for this proposed product with the addition of subheadings (e.g., Risk Summary, Human Data, and Animal Data) under the pregnancy subsection of labeling.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action

The recommendations from individual review disciplines are as follows:

- Clinical Pharmacology: Approval
- Clinical: Approval
- Pharm/Tox: Approval
- ONDQA CMC: Approval
- ONDQA Biopharm: Approval with a PMC
- CDTL Recommendation for Regulatory Action: Approval

12.2 Risk Benefit Assessment

The risk benefit was assessed in the review by Dr. Aisha Johnson dated December 26, 2013. The proposed product is bioequivalent to the reference product (Asacol tablets) in terms of mesalamine exposure. Therefore, the proposed product is expected to be at least as safe and efficacious as Asacol tablets. There is the potential for a safety advantage for the proposed product given that it does not contain DBP. Overall, it is anticipated that the benefits of the proposed product for the induction of remission and the maintenance of remission of UC outweigh the risks of the product in the appropriate adult patient population.

12.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No REMS is recommended with this application.

12.4 Recommendation for Postmarketing Required Pediatric Studies

The proposed product is a new dosage form. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. DGIEP consulted PMHS and reached consensus on PREA requirements. The reader is referred to PMHS review by Dr. Erica Radden for details.

A PeRC meeting was held on January 9, 2013. The PeRC committee concurred with DGIEP decision on the following:

- Waiver of studies in patients <5 years: This is because studies in this age group are impossible or highly impractical due to the small number of ulcerative colitis patients who are less than 5 years of age.
- Deferral of studies in patients 5-17 years of age.

The Applicant is required to conduct the following studies as postmarketing requirements.

Clinical Study 1:

A randomized, double-blind study in pediatric patients aged 5 to 17 years with active mild to moderate ulcerative colitis (UC) 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.

Protocol Submission Date: 8/31/2013
Study Completion Date: 5/31/2015
Final Report Submission: 9/30/2015

Clinical Study 2:

A randomized, double-blind study in pediatric patients ages 5 to 17 years using an age-appropriate formulation for the maintenance of remission of UC.

Protocol Submission Date: 8/31/2013
Study Completion Date: 5/31/2016
Final Report Submission: 9/30/2016

As noted in Section 9 of this document, the Applicant has conducted three pediatric studies (b) (4)

12.5 Recommendation for other Postmarketing Study Requirements (PMRs)

None (except for the PREA required pediatric studies described in Section 12.4)

12.6 Recommendation for Postmarketing Study Commitments (PMCs)

PMCs related to dissolution data and specification: The reader is referred to the ONDQA Biopharm reviews by Dr. John Duan dated December 28, 2012, and January 12, 2013.

Warner Chilcott agrees to the following post marketing commitment to further evaluate the dissolution specification and submit a supplement to the NDA.

- Collect additional dissolution profile data (including the additional 75 min time point, n=12) from the stability batches at the scheduled time points and from at least (b) (4) batches manufactured during the first year after action date. These data will be used to set the final dissolution acceptance criteria.
- Provide a report with the complete dissolution information/data under a supplement to the NDA within (b) (4) from action date.

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

/s/

SUE CHIH H LEE
02/01/2013