CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204412Orig1s006

Trade Name:	DELZICOL
Generic or Proper Name:	mesalamine
Sponsor:	Allergan Pharmaceuticals International LTD
Approval Date:	september 9, 2015
Indication:	DELZICOL is an aminosalicylate indicated for: • Treatment of mildly to moderately active ulcerative colitis in patients 5 years of age older • Maintenance of remission of ulcerative colitis in adults

CENTER FOR DRUG EVALUATION AND RESEARCH

204412Orig1s006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204412/S-006

SUPPLEMENT APPROVAL

Warner Chilcott (US), LLC
c/o Forest Research Institute, Inc.
Attention: Betsy Kurian, PharmD
Manager, Regulatory Affairs
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Kurian:

Please refer to your Supplemental New Drug Application (sNDA) dated November 11, 2014, received November 12, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Delzicol (mesalamine) Delayed-Release Capsules, 400 mg.

We acknowledge receipt of your amendments dated January 08, 2015, February 24 and 26, 2015, May 05 and 28, 2015, June 18 and 24(3), 2015, July 01 and 13, 2015, August 12, 13, 14, 25, 31, and September 08, 2015.

This "Prior Approval" supplemental new drug application provides for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content

of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your August 13, 2015, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

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.

Because none of these criteria apply to this supplemental application, you are exempt from this requirement.

We remind you that PMR 2011-2 from your February 1, 2013 approval letter regarding maintenance of remission of ulcerative colitis is not yet fulfilled. This post-marketing requirement is listed below.

> 2011-2 A randomized, double-blind study in pediatric patients ages 5 to 17 years using an age-appropriate formulation for the maintenance of remission of ulcerative colitis.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We note that you have fulfilled the pediatric study requirement for the treatment of mildly to moderately active ulcerative colitis in pediatric patients ages 5 to 17 years listed below:

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

> OPDP Regulatory Project Manager
> Food and Drug Administration
> Center for Drug Evaluation and Research
> Office of Prescription Drug Promotion (OPDP)
> 5901-B Ammendale Road
> Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, contact Kelly Richards, Regulatory Project Manager, at (240) 402-4276.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, MD, FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

ANDREW E MULBERG
09/09/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DELZICOL safely and effectively. See full prescribing information for DELZICOL.

DELZICOL (mesalamine) delayed-release capsules, for oral use
Initial U.S. Approval: 1987

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	09/2015
Dosage and Administration (2)	10/2014,09/2015

----------INDICATIONS AND USAGE----------

DELZICOL is an aminosalicylate indicated for:

- Treatment of mildly to moderately active ulcerative colitis in patients 5 years of age older (1.1)
- Maintenance of remission of ulcerative colitis in adults (1.2)

----------DOSAGE AND ADMINISTRATION----------

Important Administration Instructions (2 1):

- Two DELZICOL 400 mg capsules have not been shown to be interchangeable or substitutable with one mesalamine delayed-release 800 mg tablet.
- Evaluate renal function prior to initiation of DELZICOL.
- Take with or without food.
- Swallow the capsules whole; do not cut, break, crush or chew.
- For patients who are unable to swallow the capsules, the capsules can be opened and the inner tablets swallowed.

Treatment of Mildly to Moderately Active Ulcerative Colitis (2.2):

- Adults: 800 mg (two 400 mg capsules) three times daily for 6 weeks
- Pediatric Patients 5 years or older: See weight-based dosing table in the full prescribing information; twice daily dosing for 6 weeks

Maintenance of Remission of Ulcerative Colitis (2.3)

- Adults: 1.6 grams (four 400 mg capsules) daily, in two to four divided doses

----------DOSAGE FORMS AND STRENGTHS----------

Delayed-release capsules (containing four 100 mg tablets): 400 mg (3)

----------CONTRAINDICATIONS----------

Known or suspected hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of DELZICOL capsules (4, 5.3)

----------WARNINGS AND PRECAUTIONS----------

- Renal Impairment: Evaluate the risks and benefits of using DELZICOL in patients with known renal impairment or taking nephrotoxic drugs; monitor renal function (5.1, 7.1, 8.6, 13.2)
- Mesalamine-induced Acute Intolerance Syndrome: Symptoms may be difficult to distinguish from an ulcerative colitis exacerbation; monitor for worsening symptoms while on treatment; discontinue treatment, if acute intolerance syndrome suspected (5 2)
- Hypersensitivity Reactions, including myocarditis and pericarditis: Evaluate patients immediately and discontinue DELZICOL, if a hypersensitivity reaction is suspected (5.3)
- Hepatic Failure Evaluate the risks and benefits of using DELZICOL in patients with known liver impairment (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥5%) are

- Adults: eructation, abdominal pain, constipation, dizziness, rhinitis, back pain, and rash (6.1)
- Pediatrics: nasopharyngitis, headache, abdominal pain, dizziness, sinusitis, rash, cough and diarrhea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-521-8813 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------

- Nephrotoxic Agents including NSAIDs: Increased risk of nephrotoxicity; monitor for changes in renal function and mesalamine-related adverse reactions. (7.1)
- Azathioprine or 6-Mercaptopurine: Increased risk of blood disorders; monitor complete blood cell counts and platelet counts (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Geriatric Patients: Increased risk of blood dyscrasias; monitor complete blood cell counts and platelet counts (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised 09/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Mildly to Moderately Active Ulcerative Colitis

DELZICOL® is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

1.2 Maintenance of Remission of Ulcerative Colitis

DELZICOL® is indicated for the maintenance of remission of ulcerative colitis in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Two DELZICOL 400 mg capsules have not been shown to be interchangeable or substitutable with one mesalamine delayed-release 800 mg tablet.
- Evaluate renal function prior to initiation of DELZICOL
- Take DELZICOL capsules with or without food.
- Swallow the capsules whole; do not cut, break, crush or chew the capsules.
- For patients who are unable to swallow the capsules whole, carefully open the capsule(s) and swallow the contents (four 100 mg tablets).
    - Open the number of capsules required to make up a complete dose *[see Dosage and Administration (2.2, 2.3)]*.
    - There are 4 tablets per capsule. Ensure all tablets per capsule are swallowed and no tablets are retained in the mouth.
    - Swallow the tablets whole; do not cut, break, crush or chew the tablets.
- Intact, partially intact, and/or tablet shells have been reported in the stool; Instruct patients to contact their physician if this occurs repeatedly. Protect DELZICOL capsules from moisture. Close the container tightly and leave any desiccant pouches present in the bottle along with the tablets.

2.2 Dosage for Treatment of Mildly to Moderately Active Ulcerative Colitis

Adults
For adults, the recommended dosage of DELZICOL is 800 mg (two 400 mg capsules) three times daily (total daily dosage of 2.4 grams) for a duration of 6 weeks *[see Clinical Studies (14.1)]*.

Pediatrics
For pediatric patients 5 years of age and older, the recommended total daily dosage of DELZICOL is weight-based (up to maximum of 2.4 grams per day) divided into two daily doses for a duration of 6 weeks (see Table 1).

Table 1. Pediatric Dosage by Weight

Weight Group (kg)	Daily Dosage (mg/kg/day)	Maximum Daily Dosage (grams per day)	Morning Dosage	Afternoon Dosage
17 to 32	36 to 71	1.2	two 400 mg capsules	one 400 mg capsules
33 to 53	37 to 61	2	three 400 mg capsules	two 400 mg capsules
54 to 90	27 to 44	2.4	three 400 mg capsules	three 400 mg capsules

2.3 Dosage for Maintenance of Remission of Ulcerative Colitis

The recommended dosage of DELZICOL in adults is 1.6 grams (four 400 mg capsules) daily in two to four divided doses.

3 DOSAGE FORMS AND STRENGTHS

DELZICOL (mesalamine) delayed-release capsules are clear capsules and imprinted "WC 400mg" in black ink. Each capsule contains four reddish-brown coated 100 mg mesalamine tablets.

4 CONTRAINDICATIONS

DELZICOL is contraindicated in patients with known or suspected hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of DELZICOL *[see Warnings and Precautions (5.3), Adverse Reactions (6.2), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure, has been reported in patients taking products such as DELZICOL that contain mesalamine or are converted to mesalamine *[see Adverse Reactions (6.2)]*.

Evaluate renal function prior to initiation of DELZICOL and periodically while on therapy.

Evaluate the risks and benefits of using DELZICOL in patients with known renal impairment or history of renal disease or taking concomitant nephrotoxic drugs *[see Drug Interactions (7.1), Use in Specific Populations (8.6), Nonclinical Toxicology (13.2)]*.

5.2 Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash. Monitor

patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with DELZICOL.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some patients may have a similar reaction to DELZICOL or to other compounds that contain or are converted to mesalamine.

As with sulfasalazine, mesalamine-induced hypersensitivity reactions may present as internal organ involvement, including myocarditis, pericarditis, nephritis, hepatitis, pneumonitis, and hematologic abnormalities. Evaluate patients immediately if signs or symptoms of a hypersensitivity reaction are present. Discontinue DELZICOL if an alternative etiology for the signs or symptoms cannot be established.

5.4 Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Evaluate the risk and benefits of using DELZICOL in patients with known liver impairment.

6 ADVERSE REACTIONS

The most serious adverse reactions seen in DELZICOL clinical trials or with other products that contain or are metabolized to mesalamine are:

- Renal Impairment *[see Warnings and Precautions (5.1)]*
- Mesalamine-Induced Acute Intolerance Syndrome *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Hepatic Failure *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of DELZICOL has been established based on adequate and well-controlled studies of mesalamine delayed-release tablets. In total, mesalamine delayed-release 400 mg tablets have been evaluated in 2690 patients with ulcerative colitis in controlled and open-label trials. Below is a description of the adverse reactions of mesalamine delayed-release tablets in these adequate and well-controlled studies.

Clinical studies supporting mesalamine delayed-release tablets use for the treatment of mildly to moderately active ulcerative colitis included two 6-week, placebo-controlled, randomized, double-blind studies in adults with mildly to moderately active ulcerative colitis (Studies 1 and 2), and one 6-week, randomized, double-blind, study of 2 dosage levels in children with mildly to moderately active ulcerative colitis (Study 3). Clinical studies supporting the use of mesalamine delayed-release tablets in the maintenance of remission of ulcerative colitis included a 6-month, randomized, double-blind, placebo-controlled, multi-center study (Study 4) and four active-controlled maintenance trials comparing mesalamine delayed-release with sulfasalazine. Mesalamine delayed-release tablets have been evaluated in 427 adults and 107 children with ulcerative colitis in these controlled studies.

Treatment of Mildly to Moderately Active Ulcerative Colitis

Adults
In a 6-week placebo-controlled clinical study (Study 1) involving 105 patients, 53 of whom were randomized to mesalamine delayed-release tablets 2.4 grams per day *[see Clinical Studies (14.1)]*, 4% of the mesalamine delayed release tablets -treated patients in 2.4 grams per day group discontinued therapy because of adverse reactions as compared to 0% of the placebo-treated patients. The average age of patients was 41 years and 49 % of patients were male. Adverse reactions leading to withdrawal from mesalamine delayed-release tablets included (each in one patient): diarrhea and colitis flare; dizziness, nausea, joint pain, and headache.

The most common adverse reactions in patients treated with mesalamine delayed release tablets 2.4 grams per day in Study 1 are listed in Table 2 below.

Table 2. Most Common Adverse Reactions Reported in Study 1 for the Treatment of Mild to Moderate Ulcerative Colitis in Adults*

Adverse Reaction	% of Patients with Adverse Reactions	
	Mesalamine Delayed release 2.4 grams per day	Placebo
	(n = 53)	(n = 52)
Eructation	26	19
Abdominal pain	21	12
Constipation	11	0
Dizziness	9	8
Rhinitis	8	6
Back pain	6	4
Rash	6	4
Dyspepsia	4	0
Flu syndrome	4	2

* At Least 2% of Patients in the Mesalamine Delayed Release Tablets Group and at a Rate Greater than Placebo

Pediatric Patients 5 to 17 Years Old
A randomized, double-blind, 6-week study of 2 dosage levels of mesalamine delayed-release 400 mg tablets (Study 3) was conducted in 82 pediatric patients 5 to 17 years of age with mildly to moderately active ulcerative colitis. All patients were divided by body weight category (17 to less than 33 kg, 33 to less than 54 kg, and 54 to 90 kg) and randomly assigned to receive a low dosage (1.2, 2, and 2.4 grams per day for the respective body weight category) or a high dosage (2.0, 3.6, and 4.8 grams per day).

The high dosage regimen is not recommended because it was not found to be more effective than the recommended low dosage regimen *[see Dosage and Administration (2.2), Clinical Studies (14.1)]*.

Duration of exposure to mesalamine among the 82 patients in the study ranged from 12 to 50 days (mean of 40 days in each dosage group). The majority (88%) of patients in each group were treated for more than 5 weeks. Table 3 provides a summary of the specific reported adverse reactions.

Table 3. Adverse Reactions ≥ 5% Reported in Study 3 for the Treatment of Mild to Moderate Ulcerative Colitis in Pediatric Patients*		
Adverse Reaction	% of Patients with Adverse Reactions	
	Low Dosage	High Dosage
	(n=41)	(n=41)
Nasopharyngitis	15	12
Headache	10	5
Abdominal pain	10	2
Dizziness	7	2
Sinusitis	7	0
Rash	5	5
Cough	5	0
Diarrhea	5	0
Fatigue	2	10
Pyrexia	0	7
Increased Lipase	0	5
Low Dosage = mesalamine 400 mg delayed-release tablet 1.2 to 2.4 grams/day; High Dosage = mesalamine 400 mg delayed-release tablet 2.0 to 4.8 grams/day. Dosage was dependent on body weight. Adverse Reactions reported at the 1-week telephone follow-up visit are included.		

* At Least 5% of Patients in the low dosage or high dosage group

Twelve percent of the patients in the low dosage group (5 patients) and 2% of the patients in the high dosage group (1 patient) had serious adverse reactions. The serious adverse reactions consisted of sinusitis, adenovirus infection, and pancreatitis in one patient each in the low dosage group. Abdominal pain and decreased body mass index occurred in one patient and bloody diarrhea and sclerosing cholangitis also occurred in one patient in the low dosage group. Anemia and syncope occurred in one patient in the high dosage group.

Five patients were withdrawn from the study due to adverse reactions: 3 (7%) in the low dosage group (1 patient each with adenovirus infection, sclerosing cholangitis, and pancreatitis) and 2 patients (5%) in the high dosage group (1 patient with increased amylase and increased lipase, and 1 patient with upper abdominal pain).

In general, the nature and severity of reactions in the pediatric population was similar to those reported in adult populations of patients with ulcerative colitis.

Maintenance of Remission of Ulcerative Colitis

Clinical studies supporting the use of mesalamine delayed release tablets in the maintenance of remission of ulcerative colitis in adults included a randomized, double-blind, multi-center, placebo-controlled clinical trial of 6 months' duration in 264 patients (Study 4) *[see Clinical Studies (14.2)]*.

In Study 4, a randomized, double-blind, multi-center, placebo-controlled clinical trial of 6 months' duration, 87 patients were randomized to receive mesalamine delayed release tablets 1.6 grams per /day compared to 87 patients randomized to placebo. The average age of patients in Study 4 was 42 years and 55 % of patients were male. Adverse reactions leading to study withdrawal in patients using mesalamine delayed release tablets included (each in one patient): anxiety, stomatitis and asthenia.

In addition to the adverse reactions listed in Table 2, the following occurred at a frequency of 2% or greater in patients who received mesalamine delayed-release tablets in Study 4: abdominal enlargement, gastroenteritis, gastrointestinal hemorrhage, infection, joint disorder, nervousness, paresthesia, hemorrhoids, tenesmus, urinary frequency and vision abnormalities.

6.2 Postmarketing Experience

In addition to the adverse reactions reported above in clinical trials involving mesalamine delayed-release tablets, the adverse reactions listed below have been identified during post-approval use of mesalamine delayed-release tablets and other mesalamine-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Neck pain, facial edema, edema, lupus-like syndrome, drug fever.

Cardiovascular: Pericarditis, myocarditis *[see Warnings and Precautions (5.3)]*.

Gastrointestinal: Anorexia, pancreatitis, gastritis, increased appetite, cholecystitis, dry mouth, oral ulcers, perforated peptic ulcer, bloody diarrhea.

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy.

Musculoskeletal: Gout.

Nervous: Depression, somnolence, emotional lability, hyperesthesia, vertigo, confusion, tremor, peripheral neuropathy, transverse myelitis, Guillain-Barré syndrome.

Renal: Renal failure, interstitial nephritis, minimal change nephropathy *[see Warnings and Precautions (5.1)]*.

Respiratory/Pulmonary: Eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis.

Skin: Alopecia, psoriasis, pyoderma gangrenosus, dry skin, erythema nodosum, urticaria.

Special Senses: Eye pain, taste perversion, blurred vision, tinnitus.

Urogenital: Dysuria, urinary urgency, hematuria, epididymitis, menorrhagia, reversible oligospermia.

Laboratory Abnormalities: Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated GGT, elevated LDH, elevated bilirubin, elevated serum creatinine and BUN.

7 DRUG INTERACTIONS

7.1 Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of nephrotoxicity. Monitor patients taking nephrotoxic drugs for changes in renal function and mesalamine-related adverse reactions *[see Warnings and Precautions (5.1)]*.

7.2 Azathioprine or 6-Mercaptopurine

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine may increase the risk for blood disorders. If concomitant use of DELZICOL and azathioprine or 6-mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary
There are no adequate and well controlled studies of DELZICOL use in pregnant women. Limited published human data on mesalamine show no increase in the overall rate of congenital malformations. Some data show an increased rate of preterm birth, stillbirth, and low birth weight; however, these adverse pregnancy outcomes are also associated with active inflammatory bowel disease. Furthermore, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. No evidence of fetal harm was observed in animal reproduction studies of mesalamine in rats and rabbits at oral doses approximately 1.9 times (rat) and 3.9 times (rabbit) the recommended human dose. DELZICOL should be used during pregnancy only if clearly needed.

Human Data
Mesalamine crosses the placenta. In prospective and retrospective studies of over 600 women exposed to mesalamine during pregnancy, the observed rate of congenital malformations was not increased above the background rate in the general population. Some data show an increased rate of preterm birth, stillbirth, and low birth weight, but it is unclear whether this was due to underlying maternal disease, drug exposure, or both, as active inflammatory bowel disease is also associated with adverse pregnancy outcomes.

Animal data
Reproduction studies with mesalamine were performed during organogenesis in rats and rabbits at oral doses up to 480 mg/kg/day. There was no evidence of impaired fertility or harm to the fetus. These mesalamine doses were about 1.9 times (rat) and 3.9 times (rabbit) the recommended human dose, based on body surface area.

8.2 Lactation

Mesalamine and its N-acetyl metabolite are present in human milk. In published lactation studies, maternal mesalamine doses from various oral and rectal formulations and products ranged from 500 mg to 3 g daily. The concentration of mesalamine in milk ranged from non-detectable to 0.11 mg/L. The concentration of the N-acetyl-5-aminosalicylic acid metabolite ranged from 5 to 18.1 mg/L. Based on these concentrations, estimated infant daily doses for an exclusively breastfed infant are 0 to 0.017 mg/kg/day of mesalamine and 0.75 to 2.72 mg/kg/day of N-acetyl-5-aminosalicylic acid. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DELZICOL and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Caution should be exercised when DELZICOL is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of DELZICOL for the treatment of mildly to moderately active ulcerative colitis in pediatric patients 5 to 17 years of age has been established based on adequate and well-controlled studies using mesalamine delayed-release 400 mg tablets. Use of DELZICOL in these pediatric age groups is supported by evidence from adequate and well controlled studies of mesalamine delayed-release 400 mg tablets in adults and a single 6-week study in 82 pediatric patients 5 to 17 years of age *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*.

The safety and effectiveness of DELZICOL for the treatment of mildly to moderately active ulcerative colitis in pediatric patients below the age of 5 years have not been established. The safety and effectiveness of DELZICOL in the maintenance of remission of ulcerative colitis in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of mesalamine delayed-release tablets did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Reports from uncontrolled clinical studies and postmarketing experience suggest a higher incidence of blood dyscrasias (agranulocytosis, neutropenia, pancytopenia) in subjects receiving mesalamine delayed-release tablets who are 65 years or older compared to younger patients. Monitor complete blood cell counts and platelet counts in elderly patients during treatment with DELZICOL.

In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing DELZICOL *[see Use in Specific Populations (8.6)]*.

8.6 Renal Impairment

Mesalamine is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Evaluate renal function in all patients prior to initiation and periodically while on DELZICOL therapy. Monitor patients with known renal impairment or history of renal disease or taking nephrotoxic drugs for decreased renal function and mesalamine-related adverse reactions. *[see Warnings and Precautions (5.1), Drug Interactions (7.1), Adverse Reactions (6.2)]]*.

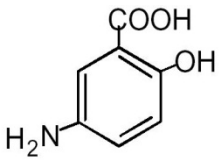
10 OVERDOSAGE

There is no specific antidote for mesalamine overdose and treatment for suspected acute severe toxicity with DELZICOL should be symptomatic and supportive. This may include prevention of further gastrointestinal tract absorption, correction of fluid electrolyte imbalance, and maintenance of adequate renal function. DELZICOL is a pH dependent delayed-release product and this factor should be considered when treating a suspected overdose.

11 DESCRIPTION

Each DELZICOL (mesalamine) delayed-release capsule for oral administration contains four 100 mg tablets of mesalamine, an aminosalicylate. DELZICOL (mesalamine) delayed-release capsules contain acrylic based resin, methacrylic acid and methyl methacrylate copolymer (Eudragit S), which dissolves at pH 7 or greater and releases mesalamine in the terminal ileum and beyond for topical anti-inflammatory

action in the colon. Mesalamine (also referred to as 5-aminosalicylic acid or 5-ASA) has the chemical name 5-amino-2-hydroxybenzoic acid. Its structural formula is:



Molecular Weight: 153.1
Molecular Formula: $C_7H_7NO_3$

Inactive Ingredients: Each capsule contains colloidal silicon dioxide, dibutyl sebacate, ferric oxide red, ferric oxide yellow, lactose monohydrate, magnesium stearate, methacrylic acid and methyl methancrylate copolymer (Eudragit S), polyethylene glycol, povidone, sodium starch glycolate, talc and hydroxypropyl methylcellulose (HPMC).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of mesalamine is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, that is, prostanoids, and through the lipoxygenase pathways, that is, leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic ulcerative colitis, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

12.3 Pharmacokinetics

Absorption
Approximately 28% of mesalamine in mesalamine delayed-release formulation is absorbed after oral ingestion. Following replicate single dose oral administration of DELZICOL 400 mg capsule containing four 100 mg tablets in healthy subjects (N = 146) under fasted conditions, the mean C_{max}, $AUC_{8\text{-}48}$ and AUC_{tldc} values were 150 ± 235 ng/mL, 640 ± 521 ng.h/mL, and 909 ± 777 ng.h/mL, respectively. The median [range] T_{max} for mesalamine following DELZICOL 400 mg capsule containing four 100 mg tablets was approximately 10 hours [5.5 – 48 hours], reflecting the delayed-release characteristics of the formulation.

A high fat meal increased systemic exposure of mesalamine (geometric mean C_{max}: ↑ 32%; $AUC_{8\text{-}48\ h}$: ↑ 46 %; AUC: ↑ 29%) and delayed the median t_{max} by approximately 4 hours compared to results in the fasted state. The observed differences in mesalamine exposure due to concomitant food intake are not considered to be clinically relevant at the total daily dosage of 2.4 grams per day.

Elimination
Metabolism
The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver to N-acetyl-5-aminosalicylic acid.

Excretion

Absorbed mesalamine is excreted mainly by the kidney as N-acetyl-5-aminosalicylic acid. Unabsorbed mesalamine is excreted in feces.

After intravenous administration, the elimination half-life of mesalamine is reported to be approximately 40 minutes. After oral dosing, the median terminal $t_{1/2}$ values for mesalamine are usually about 25 hours, but are variable, ranging from 1.5 to 296 hours. There is a large inter-subject and intra-subject variability in the plasma concentrations of mesalamine and N-acetyl-5-aminosalicylic acid and in their terminal half-lives following administration of DELZICOL.

Specific Populations
Pediatric Patients

In a dose-ranging pharmacokinetic study evaluating 30, 60 and 90 mg/kg per day doses of mesalamine delayed-release 400 mg tablets administered twice daily for four weeks, the mean C_{avg} values of mesalamine in pediatric ulcerative colitis patients ranged from approximately 400 ng/mL to 2100 ng/mL based on data from all dose levels.

In a study evaluating mesalamine delayed-release tablets in pediatric ulcerative colitis patients (Study 3), mean plasma concentrations of mesalamine (based on sparse sampling) were 820 to 988 ng/mL at the low dose level (that is, 1.2, 2 or 2.4 grams/day based on body weight strata of 17 to less than 33 kg, 33 to less than 54 kg, and 54 to 90 kg, respectively).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Mesalamine was not carcinogenic at dietary doses of up to 480 mg/kg/day in rats and 2000 mg/kg/day in mice, which are about 2.9 and 6.1 times the maximum recommended maintenance dose of DELZICOL of 1.6 grams per day or 26.7 mg/kg/day, based on 60 kg body weight, respectively, based on body surface area.

Mutagenesis
Mesalamine was negative in the Ames assay for mutagenesis, negative for induction of sister chromatid exchanges (SCE) and chromosomal aberrations in Chinese hamster ovary cells *in vitro*, and negative for induction of micronuclei (MN) in mouse bone marrow polychromatic erythrocytes.

Impairment of Fertility
Mesalamine, at oral doses up to 480 mg/kg/day (about 1.9 times the recommended human treatment dose on a body surface area basis), was found to have no effect on fertility or reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

In animal studies (rats, mice, dogs), the kidney was the principal organ for toxicity. (In the following, comparisons of animal dosing to recommended human dosing are based on body surface area and a 2.4 grams per day dose for a 60 kg person.)

Mesalamine causes renal papillary necrosis in rats at single doses of approximately 750 mg/kg to 1000 mg/kg (approximately 3 to 4 times the recommended human dose based on body surface area). Doses of 170 and 360 mg/kg/day (about 0.7 and 1.5 times the recommended human dose based on body

surface area) given to rats for six months produced papillary necrosis, papillary edema, tubular degeneration, tubular mineralization, and urothelial hyperplasia.

In mice, oral doses of 4000 mg/kg/day mesalamine (approximately 8 times the recommended human dose based on body surface area) for three months produced tubular nephrosis, multifocal/diffuse tubulo-interstitial inflammation, and multifocal/diffuse papillary necrosis.

In dogs, single doses of 6000 mg (approximately 8 times the recommended human dose based on body surface area) of delayed-release mesalamine tablets resulted in renal papillary necrosis but were not fatal. Renal changes have occurred in dogs given chronic administration of mesalamine at doses of 80 mg/kg/day (1.1 times the recommended human dose based on body surface area).

14 CLINICAL STUDIES

The safety and efficacy of DELZICOL has been established based on adequate and well-controlled studies of mesalamine delayed-release tablets. Below is a description of the results of the adequate and well-controlled studies of mesalamine delayed-release tablets for the treatment of mildly to moderately active ulcerative colitis in adults and pediatric patients 5 to 17 years of age and the maintenance of remission of ulcerative colitis in adults.

14.1 Treatment of Mildly to Moderately Active Ulcerative Colitis

Adults

Two placebo-controlled studies (Studies 1 and 2) have demonstrated the efficacy of mesalamine delayed-release tablets in patients with mildly to moderately active ulcerative colitis.

In one randomized, double-blind, multi-center, placebo-controlled clinical trial of 6 weeks' duration in 158 patients (Study 1), patients received mesalamine delayed release dosages of 1.6 grams per day (800 mg twice a day; n=53) and 2.4 grams per day (800 mg three times a day; n=53), compared to placebo (n=52). The scoring system for determination of treatment efficacy included assessment of stool frequency, rectal bleeding, sigmoidoscopic findings, patient's functional assessment, and physician global assessment. At the dosage of 2.4 grams per day, 21 of 43 (49%) patients using mesalamine delayed release tablets showed an improvement in sigmoidoscopic appearance of the bowel compared to 12 of 44 (27%) patients using placebo ($p = 0.048$). In addition, significantly more patients in the mesalamine delayed release tablets 2.4 grams per day group showed improvement in rectal bleeding and stool frequency. The 1.6 grams per day dosage regimen is not recommended because it did not produce consistent evidence of effectiveness [see *Dosage and Administration (2.2*)].

In a second randomized, double-blind, placebo-controlled clinical trial of 6 weeks' duration in 87 patients (Study 2), patients received mesalamine delayed release tablets of 1.6 grams per day (400 mg four times a day; n=11) and 4.8 grams per day (1.2 grams four times a day; n=38), compared to placebo four times a day (n=38). mesalamine delayed release tablets 4.8 grams per day for 6 weeks resulted in sigmoidoscopic improvement in 28 of 38 (74 %) patients compared to 10 of 38 (26 %) placebo patients (p less than 0.001). Also, more patients in the mesalamine delayed release tablets 4.8 grams per day group than the placebo group showed improvement in overall symptoms. The 4.8 grams per day dosage regimen is not recommended because greater efficacy was not demonstrated with this dosage compared to the 2.4 grams per day dosage *[see Dosage and Administration (2.2)]*.

Pediatrics

The safety and effectiveness of mesalamine delayed release in pediatric patients 5 to 17 years of age for treatment of mildly to moderately active ulcerative colitis are supported by evidence from adequate and well controlled studies of mesalamine delayed release in adults and a single study in pediatric patients.

A randomized, double-blind, 6-week study of two dosage levels of mesalamine delayed release tablets (Study 3) was conducted in 82 pediatric patients 5 to 17 years of age with mildly or moderately active ulcerative colitis defined as a score of 10 to 55 on the Pediatric Ulcerative Colitis Activity Index (PUCAI) (which includes assessment of abdominal pain, rectal bleeding, stool consistency, number of stools per 24 hours, presence of nocturnal bowel movement and activity level, and has a total maximum score of 85; each of the subscales are scored from 0 to 10 except rectal bleeding which is scored from 0 to 30, and number of stools per 24 hours which is scored from 0 to 15) and rectal bleeding and stool frequency Mayo subscale scores of ≥1 (each of these subscales are scored from zero (normal) to three (most severe)).[1,2]

All patients were divided by weight category (17 to less than 33 kg, 33 to less than 54 kg, and 54 to 90 kg) and randomly assigned to receive a low dosage (1.2, 2, and 2.4 grams per day for the respective weight category) or a high dosage (2, 3.6, and 4.8 grams per day). Doses were administered every 12 hours.

The proportion of patients who achieved success based on the Truncated Mayo Score (TM-Mayo) (based on the stool frequency and rectal bleeding subscores of the Mayo Score) and based on the PUCAIwas measured after 6 weeks of treatment. Success based on TM-Mayo was defined as either partial response (improvement from baseline in stool frequency or rectal bleeding subscores with no worsening in the other) or complete response (both stool frequency and rectal bleeding subscores equal 0). Success based on PUCAI was defined as either partial response (PUCAI reduction of greater than or equal to 20 points from Baseline to Week 6 with Week 6 score greater than or equal to 10) or complete response (PUCAI less than 10 at Week 6).

There were 41 patients in the low dosage group and 41 patients in the high dosage group who received at least one dose of mesalamine delayed-release 400 mg tablets; 36 patients in each dosage group completed the study. Patients were considered treatment failures if they did not achieve success or dropped out due to adverse reaction or lack of efficacy.

At Week 6, 73% of the patients in the low dosage group, and 70% of the patients in the high dosage group achieved success based on the TM-Mayo; 34% of the patients in the low dosage group and 43% of the patients in the high dosage group achieved complete response. At Week 6, 56% of the patients in the low dosage group, and 55% of the patients in the high dosage group achieved success based on the PUCAI; 46% of the patients in the low dosage group and 43% of the patients in the high dosage group achieved complete response.

The high dosage regimen is not recommended because it was not more effective than the low dosage regimen *[see Dosage and Administration (2.2)]*.

14.2 Maintenance of Remission of Ulcerative Colitis

Adults

In a randomized, double-blind, multi-center, placebo-controlled clinical trial of 6 months' duration in 264 patients (Study 4), patients received mesalamine delayed-release tablets of 0.8 grams per day (400 mg twice a day; n = 90) and 1.6 grams per day (400 mg four times a day; n = 87), compared to placebo four

times a day (n = 87). The proportion of patients treated with 0.8 grams per day who maintained endoscopic remission was not statistically significant compared to placebo; the 0.8 grams per day dosage regimen is not recommended *[see Dosage and Administration (2.3)]*. The number of patients using mesalamine delayed-release tablets 1.6 grams per day who maintained endoscopic remission of ulcerative colitis was 61 of 87 (70%) compared with 42 of 87 (48%) of placebo patients (p = 0.005).

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

15 REFERENCES

1. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: A prospective multicenter study. Gastroenterology. 2007;133:423–432.

2. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. *N Engl J Med*. 1987;317(26):1625-9.

16 HOW SUPPLIED/STORAGE AND HANDLING

DELZICOL (mesalamine) delayed-release capsules are available as clear capsules and imprinted with "WC 400mg" in black ink. Each capsule contains four reddish-brown coated 100 mg mesalamine tablets.

NDC 0430-0854-27 Bottle of 180 capsules

Store at controlled room temperature 20° to 25° C (68° to 77° F); excursions are permitted 15° to 30° C (59° to 86° F). [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

Administration

- Inform patients that if they are switching from a previous oral mesalamine therapy to DELZICOL to discontinue their previous oral mesalamine therapy and follow the dosing instructions for DELZICOL. Inform patients that two DELZICOL 400 mg capsules cannot be substituted for one mesalamine delayed-release 800 mg tablet.
- Inform patients that DELZICOL capsules can be taken with or without food.
- Instruct patients to swallow the DELZICOL capsules whole. Do not cut, break, crush or chew the capsules.
- For patients who are unable to swallow the capsules whole, carefully open the capsules and swallow the contents (four 100 mg tablets).
    - Open the number of capsules required to make up a complete dose.
    - There are 4 tablets per capsule. Ensure all tablets per capsule are swallowed and no tablets are retained in the mouth.
    - Swallow the tablets whole; do not cut, break, crush or chew the tablets.
- Inform patients that intact, partially intact, and/or tablet shells have been reported in the stool. Instruct patients to contact their physician if this occurs repeatedly.
- Instruct patients to protect DELZICOL capsules from moisture. Instruct patients to close the container tightly and to leave any desiccant pouches present in the bottle along with the capsules.

Renal Impairment

- Inform patients that DELZICOL may decrease their renal function, especially if they have known renal impairment or are taking nephrotoxic drugs, and periodic monitoring of renal function will be performed while they are on therapy. Advise patients to complete all blood tests ordered by their physician.

Mesalamine-Induced Acute Intolerance Syndrome

- Instruct patients to report to their physician if they experience new or worsening symptoms of cramping, abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash.

Hypersensitivity Reactions

- Inform patients of the signs and symptoms of hypersensitivity reactions, and advise them seek immediate medical care should signs and symptoms occur.

Hepatic Failure

- Inform patients with known liver disease of the signs and symptoms of worsening liver function and advise them to report to their physician if they experience such signs or symptoms.

Blood Disorders

- Inform elderly patients and those taking azathioprine or 6-mercaptopurine of the risk for blood disorders and the need for periodic monitoring of complete blood cell counts and platelet counts while on therapy. Advise patients to complete all blood tests ordered by their physician.

Manufactured By:
Warner Chilcott Deutschland GmbH
D-64331 Weiterstadt
Germany

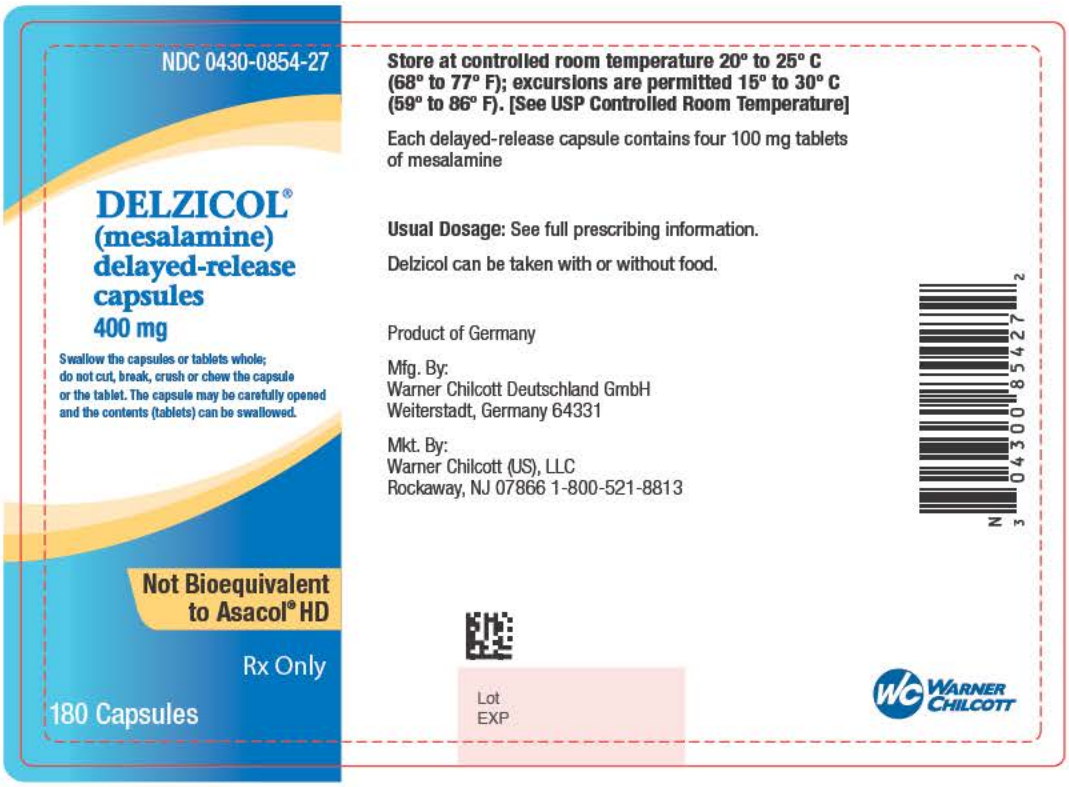
Distributed By:
Actavis Pharma, Inc.
Parsippany, NJ 07054
USA


Store at controlled room temperature 20° to 25° C (68° to 77° F); excursions are permitted 15° to 30° C (58° to 86° F). [See USP Controlled Room Temperature]
Each delayed-release capsule contains four 100 mg tablets of mesalamine
Usual Dosage: See full prescribing information.
Delzicol can be taken with or without food.
Product of Germany
Mfg. By:
Warner Chilcott Deutschland GmbH
Weiterstadt, Germany 64331
Mkt. By:
Warner Chilcott (US), LLC
Rockaway, NJ 07866 1-800-521-8813
To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-521-8813 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
311791
DELZICOL®
(mesalamine)
delayed-release
capsules
400 mg
NDC 0430-0854-95
DELZICOL®
(mesalamine)
delayed-release
capsules
400 mg
Swallow the capsules or tablets whole; do not cut, break, crush or chew the capsule or the tablet. The capsule may be carefully opened and the contents (tablets) can be swallowed.
Not Bioequivalent to Asacol® HD
SAMPLE-Not for Sale
12 Capsules
Rx Only
DELZICOL®
(mesalamine)
delayed-release
capsules
400 mg

(b) (4)


Store at controlled room temperature 20° to 25° C (68° to 77° F); excursions are permitted 15° to 30° C (59° to 86° F). [See USP Controlled Room Temperature]
Each delayed-release capsule contains four 100 mg tablets of mesalamine
Usual Dosage: See full prescribing information.
Delzicol can be taken with or without food.
NDC 0430-0854-95
Rx Only
SAMPLE-Not for Sale
DELZICOL®
(mesalamine)
delayed-release capsules
400 mg
Swallow the capsules or tablets whole; do not cut, break, crush or chew the capsule or the tablet. The capsules may be carefully opened and the contents (tablets) can be swallowed.
Not Bioequivalent to Asacol® HD
12 Capsules
Mfg. By:
Warner Chilcott Deutschland GmbH
Weiterstadt, Germany 64331
Mkt. By: Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-2513
TBD
Product of Germany
Lot
EXP

(b) (4)


NDC 0430-0854-27
DELZICOL®
(mesalamine)
delayed-release
capsules
400 mg
Swallow the capsules or tablets whole; do not cut, break, crush or chew the capsule or the tablet. The capsule may be carefully opened and the contents (tablets) can be swallowed.
Not Bioequivalent to Asacol® HD
Rx Only
180 Capsules
Store at controlled room temperature 20° to 25° C (68° to 77° F); excursions are permitted 15° to 30° C (59° to 86° F). [See USP Controlled Room Temperature]
Each delayed-release capsule contains four 100 mg tablets of mesalamine
Usual Dosage: See full prescribing information.
Delzicol can be taken with or without food.
Product of Germany
Mfg. By:
Warner Chilcott Deutschland GmbH
Weiterstadt, Germany 64331
Mkt. By:
Warner Chilcott (US), LLC
Rockaway, NJ 07866 1-800-521-8813
Lot
EXP
WARNER CHILCOTT


(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

SUMMARY REVIEW

Deputy Director Signatory Review
Andrew E. Mulberg, MD, FAAP
September 9, 2015

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA #	NDA 204412 S-006
Applicant Name	Warner Chilcott
Date of Submission	12 November 2014
PDUFA Goal Date	11 September 2015
Proprietary Name / Established (USAN) Name	Delzicol/Mesalamine
Dosage Forms / Strength	Delayed release capsules/ 400 mg (4 x 100 mg tablets)
Proposed Indication(s)	Treatment of mildly to moderately active ulcerative colitis (UC) in patients 5 years and older
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Marjorie Dannis, MD
CDTL Review	Sue-Chih Lee, Ph.D
CMC Statistics Reviewer	Zhuang Miao, Ph.D.
Clinical Pharmacology Team Leader	Sue-Chih Lee, Ph.D.
Reviewer Acting Quality Assessment Lead Acting Quality Branch Chief	Vincent(Peng) Duan, Ph.D. Kelly M. Kitchens, Ph.D. Tapash Ghosh, Ph.D.
Clinical Pharmacology Reviewer	Sandhya Apparaju, Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

In this NDA supplement, the applicant proposes to market Delzicol 400 mg delayed release tablet for the following indication:

1) Treatment of mildly to moderately active ulcerative colitis (UC) in patients 5 years and older

Currently, Warner Chilcott markets mesalamine (Asacol, Asacol HD) for the treatment of ulcerative colitis in adults. Asacol (NDA 19-651) and Asacol HD (NDA 21-830) delayed release tablets of 400 and 800 mg mesalamine have been approved for use in adults for the treatment of mildly to moderately active UC and moderately active UC, respectively. With the approval of Asacol HD in 2005, the sponsor was required to fulfill a PREA requirement of conducting a study in pediatrics and developing an age appropriate formulation. To fulfill the PREA requirement for Delzicol capsules (400 mg), the Applicant developed WC3079 capsule, a mesalamine delayed-released capsule in a phthalate free formulation, which contains four 100 mg mesalamine tablets and is intended for use in patients 5 years and older. With this submission, the Sponsor is providing the results of a relative bioavailability and palatability study to fulfill their PREA requirement (b) (4) in pediatric patients 5- 17 years of age with mildly to moderately active ulcerative colitis.

In this current application the Sponsor submitted two studies to complete the PMR for development of a new pediatric formulation. These include: Study PR-07513 (Relative Bioavailability Study) which was a single-center, open-label, randomized, single-dose, replicate treatment, 5-period, 4-sequence, 2-formulation crossover study conducted under in 160 healthy male and female volunteers. All subjects received Treatment 1 twice, Treatment 2 twice, and Treatment 3 once.

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

Subjects were randomly assigned to one of four treatment sequences:

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

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

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

All subjects were asked to swallow 8 placebo tablets as contained in two WC3079 placebo capsules. The studies submitted for review in this NDA Supplement are illustrated in the Table 1 below:

Table 1: Studies for Review in NDA Supplement: Reproduced from Dr. Dannis, Medical Review

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

I have concluded that there is sufficient evidence of clinical benefit to justify acceptance of this PMR as fulfilled without additional key information including study in the age groups that exhibit concern for palatability and choking risk. I do agree that the indication for Delzicol should be labeled accordingly to include: **Treatment of mildly to moderately active ulcerative colitis in Pediatric patients 5-17 years old**. My review will focus on the salient issues related to this risk/benefit assessment.

2. Background

Ulcerative colitis (UC) is defined as a chronic inflammatory process limited to the colon including rectum. Ulcerative colitis (UC) is a chronic inflammatory disease that involves the mucosal surface of the colon, resulting in diffuse friability and erosions with bleeding. Approximately 50% of adult patients have disease confined to the recto-sigmoid region (procto-sigmoiditis); in 30% it extends to the splenic flexure (left-sided colitis); and in less than 20% it extends more proximally and is referred to as extensive colitis.[1] However, the

predominant presentation of pediatric UC is extensive colitis. There is correlation between disease extent and symptom severity in both adults and children.[1] Differences in extent of endoscopically-active colonic disease and signs and symptom severity at presentation between adults and children suggest that it is important to consider whether defining pediatric specific endpoints to assess clinical outcome in pediatric UC trials is needed.

.

The local action of the drug is expected to be the same in children as in adults. Although the treatment effectiveness of Asacol might be able to be extrapolated from the adult indication to the pediatric patients due to disease pathology being the same in both age groups and the same mechanism of action of the drug, we cannot extrapolate an effective pediatric dosage for a minimally systemically absorbed and presumed locally-acting drug from adult studies. Both Asacol and the currently approved Delzicol have a pediatric UC indication: Asacol for 5-17 yrs of age and Delzicol for 12-17 yrs of age. Both the oral and suppository mesalamines act by "local action." Typically, one dosage form or dose is not prescribed for all patients in the wide pediatric age range of 5 to 17 years. The oral melamine dose is typically used is based on weight, in the range of 50 mg/kg/day. Similarly, it is likely that various dosages based on body size or age that account for systemic exposures would be important to understand the comparison to adult systemic exposure for understanding safety and tolerability. Efficacy is determined by the impact on altering mucosal inflammation and cannot be extrapolated by systemic exposure of the molecule and therefore requires a clinical efficacy endpoint or as in this scenario, justification of use of a pharmacodynamics measure that can be correlated and justified from adult UC studies.

The table below summarizes the regulatory activity of Delzicol, Asacol, and Asacol HD pertinent to the current efficacy supplement:

[1] Hyams J, Davis P, Lerer T et al . Clinical Outcome of Ulcerative Proctitis in Children. J Pediatr Gastroenterol Nutr;1997;25:149-152

Table 2: Pertinent Regulatory History of Delzicol (NDA 204412), Asacol (NDA 19651)*, and Asacol HD (NDA 21830)

Date	Event
January 31, 1992	Asacol approved for treatment of mildly to moderately active UC
August 19, 1997	Asacol approved for maintenance of remission of UC
March 27, 2006	Written Request (WR) for pediatric studies for mesalamine issued
May 29, 2008	Asacol HD approved for treatment of moderately active UC
June 30, 2008	Amendment 1 to WR for pediatric studies for mesalamine issued[§]
January 20, 2011	Letter from Sponsor notifying FDA that the WR was no longer being pursued[#]
October 31, 2011	Study Report for pediatric induction study (Study 2007017) received[†]
February 24, 2012	Preliminary Responses sent to sponsor for Asacol HD Pre-sNDA Meeting[‡]
January 15, 2013	Labeling approach (Asacol HD, and Delzicol) based on Study 2007017 discussed; development of an age-appropriate formulation for Delzicol discussed.[£]
February 1, 2013	Approval of Delzicol based on demonstration of bioequivalence with Asacol.
July 30, 2013	Development of an age-appropriate formulation for Delzicol discussed.
October 18, 2013	Asacol sNDA and Asacol HD sNDA approved
April 18, 2014	Approval of WC3045 for active, mild to moderate UC in patients 12 years of age and older because the capsule size was deemed inappropriate for younger patients. PMR for Pediatrics: "2011-1 A randomized, double-blind study in pediatric patients ages 5 to 17 years with ulcerative colitis using an age-appropriate formulation to evaluate the pharmacokinetics, safety, and clinical response of pediatric patients undergoing six weeks of oral mesalamine therapy. The study should compare at least two different dose levels of mesalamine and enroll at least 40 pediatric patients in each dosing arm."

*IND 26,093
[§]The final protocol design for the pediatric induction study (Study 2007017) was based on the Amended WR issued to the sponsor on June 30, 2008.
[#] The letter also notified FDA that enrollment is being terminated in the pediatric maintenance trial (Study 2008085) before reaching the required number of subjects due to lack of eligible subjects and very slow recruitment.
[†] Study Report for the pediatric induction study (Study 2007017) was submitted under NDA 21830.
[‡] Pre-sNDA Meeting on February 28, 2012 was cancelled; preliminary responses were sent to the sponsor on February 24, 2012 (filed under NDA 21830).
[£]Meeting minutes filed under IND 26,093

Further details of regulatory history are illustrated below:

Date	**Regulatory Action(s)**
January 15, 2013	Type C Meeting FDA informed Warner Chilcott that PREA required them to manufacture an age-appropriate pediatric formulation. In addition, they needed to conduct a palatability/ability to swallow

	study to determine acceptability of the proposed formulation (WC3079). FDA informed Warner Chilcott that they must justify that the WC3079 capsule can be bridged with Asacol
February 1, 2013	FDA approved Delzicol capsules, a dibutyl phthalate (DBP) free formulation based upon demonstration of bioequivalence to the reference product Asacol 400 mg tablets.
April 28, 2014	FDA approved Delzicol capsules for the treatment of mildly to moderately active ulcerative colitis for patients *12 years of age and older*.
November 11, 2014	Current sNDA submitted

In this application the applicant proposes to market Delizcol 400 mg delayed release tablet for the treatment of mildly to moderately active ulcerative colitis in pediatric patients 5 years to 17 years of age and submits the study as a fulfillment of the PREA requirement for development of a new formulation.

3. CMC

It should be noted that because the enteric coating of Asacol and Asacol HD each contain dibutyl phthalate (DBP), and because DBP is associated with safety concerns, FDA requested that the sponsor provide information on the effects of DBP in animals and humans in the labeling of each drug, and develop new DBP-free formulations for each drug. The Pregnancy and Nursing Mothers sections of the labeling for each drug were revised on May 24, 2010. An NDA for Delzicol (a DBP-free mesalamine formulation) was submitted by Warner Chilcott, LLC on July 31, 2012, and was approved on February 1, 2013, based on the demonstration of bioequivalence with Asacol. Warner-Chilcott herein has submitted an NDA for another DBP-free mesalamine formulation and gain approval based on the demonstration of bioequivalence with Asacol HD. This current formulation is illustrated reflecting the constituents of the new formulation which consists of 4 x100 mg tablets in a capsule shell.

Figure 1: Photographic representation of Asacol 400 mg, Delzicol 400 mg and the new formulation of Delzicol 400 mg (WC3079) respectively

Size of the Applicant's Mesalamine Products

- Asacol tablet 400 mg ((b) (4) mm)
- Delzicol capsule 400 mg (WC3045; size (b) (4) capsule, (b) (4) mm)
- The proposed Delzicol 400 mg capsuls (WC3079; size (b) (4) capsule, with 4 x100 mg tablets (b) (4) mm diameter/ (b) (4) mm thickness])

4. Nonclinical Pharmacology/Toxicology

No new nonclinical study reports were submitted in this supplement. I concur with the CDTL's summary of the Nonclinical review conclusions that there are no outstanding pharm/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

a. Biopharmaceutics:

The Applicant conducted the following studies:

• A relative bioavailability study (PR-07513) to study the PK profile, food effect, and the relative bioavailability of WC3079, 4 x 100 mg, compared to the REFERENCE DRUG Asacol (mesalamine) delayed-release tablets, 400 mg.

• Biopharmaceutics studies (comparative dissolution studies and alcohol dose dumping studies) on WC3045 (approved Delzicol), WC3079, and Asacol.

As stated by the Biopharmaceutics Reviewer, Dr. Duan, the Applicant used the dissolution method per the USP monograph for mesalamine delayed release tablets. A bootstrap analysis on f2 was conducted by this Reviewer due to the high variability of drug dissolution data. Based on our f2 analysis, dissolution profiles of WC3079 100 mg single tablet (the 4x100mg whole capsule is opened and only one mini-tablet is used for dissolution test), WC3079 4x100 mg tablets, and Asacol 400 mg tablets are different. Therefore, not only is the in vitro drug release of the proposed WC3079 4x100 mg whole capsule different from the referenced drug Asacol 400 mg tablets, but the drug release of the WC3079 100 mg single tablet is also different from the 4x100mg whole capsule. After the discussion within the NDA review team,

it is believed that the major difference in dissolution is in pH 6.8 and pH 6.5 conditions, in which the drug release of WC3079 should be minimal. Therefore, the impact of the dissolution differences on clinical performance is not significant. This conclusion is supported by the small and clinically insignificant physiological differences observed in the human gastrointestinal tract for which this pH change is concluded to be of no physiological relevance.

The Applicant conducted the alcohol dose dumping study to evaluate the drug release of WC3079 4x100 mg capsules and WC3079 1x100 mg single coated tablet in the presence of various concentrations of alcohol up to 40%. Similarly as WC3045, WC3079 4 x 100 mg capsules or WC3079 1 x 100 mg single coated tablets maintain no drug release in 0.1 N HCl and pH 6.0 buffer stage, in the presence of up to 40% of alcohol. A slightly faster dissolution was shown at pH 7.2 medium in the presence of 10% alcohol or higher. However, the delayed release characteristics have not been compromised due to the zero release at Acid Stage and pH 6.0 Buffer stage. The slightly faster dissolution at pH 7.2 does not raise safety concerns.

As noted by the Biopharmaceutics Reviewer, Dr. Duan, the proposed Delzicol capsules did not pass the f2 test for dissolution at pH 6.5 which is not of concern because examination of the individual dissolution data indicated that there were less outliers for the proposed Delzicol product compared to the reference product (Asacol tablets) as the product is designed to release drug at a target pH of 7. The in vitro alcohol dose dumping studies did not raise a safety concern. The reader is referred to the reviews by Dr. Peng Duan in Panorama dated August 5, 2015, for more details.

From the Biopharmaceutics perspective, the NDA efficacy supplement 204412 S-006 for Delzicol (mesalamine) Delayed-Release Capsules, 400 mg, is recommended for approval. This Signatory agrees with this assessment.

Clinical Pharmacology:
For further details, the reader is referred to the summary of the CDTL memorandum of Dr. Lee to appreciate the complexity of the analyses that have led to conclusions of comparative bioavailability and the labeling of Delzicol for this indication. By establishing the comparable bioavailability between the proposed product and Asacol Tablets, the pediatric indication approved for Asacol Tablets may be extended to the proposed product (WC3079). The relative bioavailability study and dissolution testing support the comparable performance of the proposed product as compared to Asacol tablets. Regarding food effect, a high fat meal increased the mesalamine systemic exposure by approximately 30-45% following administration of the proposed product. This is similar to what was observed for the approved Delzicol Capsules (WC3045). As such, the proposed product can be administered without regard to food.

The issue concerning bioequivalence of the two formulations was discussed. As noted in the CDTL memorandum, particularly in bolded language below, Dr. Lee states, "The Clinical Pharmacology Review Team met with Dr. Hae-Young Ahn, Deputy Director of Division of Clinical Pharmacology III, to discuss path forward. As the washout period was sufficient to

avoid drug concentration carryover, Dr. Ahn considered that the assumption of no period effect is reasonable while dismissing the whole dataset is not. **The Clinical Pharmacology Review Team concluded that the bioavailability of the proposed Delzicol Capsules 400 mg (WC3079) is comparable to that for the Asacol Tablets 400mg. However, the proposed product is not considered bioequivalent to the reference product and the label will not state interchangeability between the proposed Delzicol (WC3079) and the approved Delzicol product (WC3045) since the dissolution testing did not show robust similarity and the bioavailability analysis involves the assumption of no period effect even though that is considered a reasonable assumption.**"

This Signatory agrees with the approval recommendation of the Clinical Pharmacology reviewer and CDTL, Dr. Lee. From a practitioner perspective, it is likely that the availability of a comparatively bioavailable formulation of Delzicol which will be formulated to accommodate smaller individual drug product constitution will be instrumental positively to improve compliance with treatment. I am hopeful that post marketing surveys will be pursued to address this potential impact since this to be approved formulation will be more acceptable likely to the pediatric population. Details of swallowability are discussed below.

6. Clinical Microbiology

No new review issues are identified.

7. Clinical/Statistical-Efficacy

The Sponsor was notified of assessing the palatability of the current formulation and its suitability for the pediatric population. The Applicant was given a recommendation to conduct a palatability/swallowability study for the following reasons:

- to delineate the pediatric subpopulations that can reasonably swallow this size (b) (4) capsule,
- to provide information on patient compliance with this alternative dosing method
- to provide information that might help anticipate dosing errors and could be used to inform labeling.

From previous regulatory history, Delzicol is a larger capsule (size (b) (4) mm) compared to Asacol (size (b) (4) mm) and young children may not be able to swallow the larger capsule. The Clinical Reviewer further noted that other medications, such as Strattera and Trokendi XR, are available in size (b) (4) capsules and are approved for pediatric patients as young as 6 years of age. In contrast to Delzicol, both Strattera and Trokendi XR are approved in smaller sized tablets/capsules, which provide patients and prescribers with additional options. Development of an age-appropriate formulation for Delzicol is ongoing. Currently, there is no available information on the swallowability of the current Delzicol formulation in pediatric patients.

Study PR-00514 was a single-center, open-label, single-dose study conducted in 60 healthy children aged 5 to 11 years to characterize the swallowability of placebo tablets contained in WC3079 capsules in these children. All subjects were asked to swallow 8 placebo tablets as contained in two WC3079 placebo capsules. All 60 healthy children (30 females and 30 males) completed the study.

Results: Overall, 42 (70%) of the children swallowed all 8 tablets.

- 7 -11 years olds: 85% (34/40) swallowed 8 tablets
  10% (4/40) swallowed 0 tablets (2 patients swallowed 1 tablet)
- 5- 6 year olds: 40% (8/20) swallowed 8 tablets
  45% (9/20) swallowed 0 tablets
  (1 patient swallowed 1 tablet; 2 patients swallowed 2)
- Most children swallowed the tablets in < 5 minutes
  - 3 children swallowed 1 additional tablet between 5 and 10 minutes after administration

From this review, the most interesting data (Figure 2 below) reflect the following aspects of swallowability from Study PR-00514:

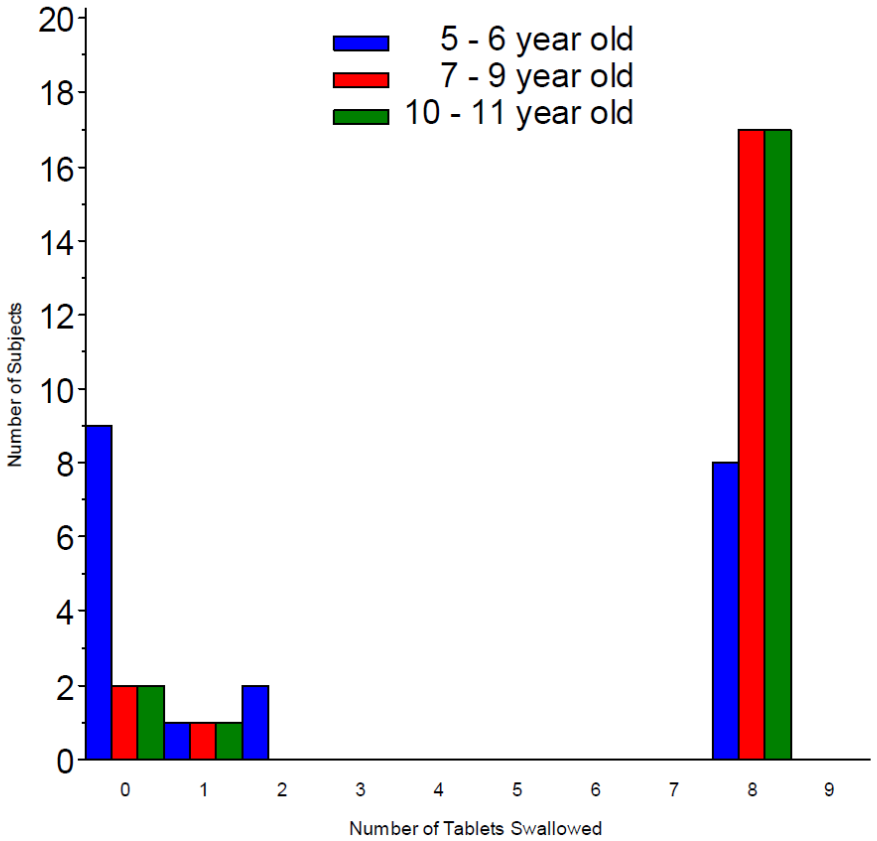


Figure 2: Swallowability Asssessment in Pediatric Subjects, Study PR-00514
Reproduced from Dr. Dannis medical summary

Dr. Dannis notes that "the size of the 100 mg tablets (inside the capsule) is clearly smaller than the Asacol 400 mg tablet which is currently approved for patients down to 5 years of age. Therefore, the results above show that WC3079 may be an age-appropriate formulation. The ability of children to take this pediatric formulation can be further assessed in a future pediatric maintenance trial wherein a study design that allows for training of the patients should be included in the protocol." The data are striking to reveal that prominent failure to swallow was exhibited in the age group of most concern, specifically 5-6 years of age. This age group has been noted to have limited but teachable ability to swallow medications. As noted by Dr. Dannis, healthy children and children with chronic illness may react differently to the need for swallowing test article. I am concerned with the ability of the youngest patients with UC to swallow this new formulation although it clearly has been demonstrated to be mostly successful.

It has been noted that pill swallowing can be overcome with appropriate techniques and these are opportunities for training. Pill swallowing difficulties are a barrier that can be overcome with a variety of successful interventions. Patel and colleagues have recently reported that "Addressing this problem and researching more effective ways of implementing these interventions can help improve medication administration and compliance in the pediatric population. A study in adolescents with IBD reported that difficulty swallowing pills was one of the most common identified barriers in treatment adherence for adolescents with inflammatory bowel disease. The commonality of pill swallowing problems in children and its potential to have a detrimental effect on compliance and administration highlight the importance of targeted interventions to help children swallow pills.[2]

This Signatory agrees with the above assessment of PMR fulfillment but still has some outstanding concerns regarding swallowability in the youngest age child with UC. Formulation guidance on palatability assessments is critical to pediatric drug development. The EMA has published formulation guidance for the development of pediatric formulations[3]. Furthermore recent literature supports the critical investigation of palatability especially in the pediatric population. Thompson and colleagues note, "However, despite the reported importance of palatability to therapeutic adherence and compliance, there is limited scientific evidence related to the assessment of oral dosage forms, especially in the development process of pharmaceutical oral dosage forms. The VAS and facial hedonic scale are the most commonly used tools to assess palatability in pediatric populations, with no standardized assessment process or statistical analysis plan. There is a limited evidence base regarding the correlation between the palatability of oral dosage forms and treatment adherence in pediatric patients. With the growing number of compounds currently under development or reformulation for use in pediatric patients, it is advantageous for biopharmaceutical companies to consider appropriate palatability testing in the clinical development program. This

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[2] Patel A, Jacobsen L, Jhaverei R and Bradford K. Effectiveness of Pediatric Pill Swallowing Interventions: A Systematic Review. Pediatrics 2015; Volume 135, number 5, May 2015.

[3] 19 May 2011,EMA/CHMP/QWP/180157/2011,Committee for Medicinal Products for Human Use (CHMP) Guideline on Pharmaceutical Development of Medicines for Paediatric Use, Draft

assessment will assist in achieving long-term treatment adherence, resulting in improvements in overall clinical outcomes."[4]

This Signatory agrees that a critical component of swallowability and palatability assessment has been performed and agree with the conclusion of fulfillment of this PMR. This Signatory agrees that a critical component of swallowability and palatability assessment has been performed and agree with the conclusion of fulfillment of this PMR in light of proposed labeling revisions focusing on ability to open capsules and have contents swallowed which are of significantly lower diameter than any previously labeled mesalamine product. The label for the new Delzicol allows opening of a capsule to swallow individual tablets-the reader is referred to Section 2.3 of the PI (Important Administration Instructions and Section 12 of this review.

8. Safety

No new safety concerns have been noted by the Medical reviewer and due to the study design assessing swallowability, there were no specific drug related issues. The remainder of the clinical program did not reveal any new safety signals with the formulation of mesalamine.

9. Advisory Committee Meeting

There was no Advisory Committee for this application. The product is not a new molecular entity and there were no scientific issues that required discussion in an Advisory Committee.

10. Pediatrics

Dr. Erica Radden notes that the swallowability study results are inconclusive but the size of the individual tablets in the proposed capsules are obviously smaller than the Asacol tablets (**Figure 1** above). This Signatory does not agree with this assessment in toto and the reader is referred to Section7 and 13 for further discussion of this issue. The reviewer did though conclude that the PREA requirement 2011-1 is considered fulfilled.

11. Other Relevant Regulatory Issues

No issues important for this review.

12. Labeling

Section 2.3 of the PI (Important Administration Instructions) should be revised as follows:

- Swallow the capsules whole; do not cut, break, crush or chew the capsules.
- For patients who are unable to swallow the capsules whole, carefully open the capsule(s) and swallow the contents (four 100 mg tablets).

[4] A Systematic Literature Review on the Assessment of Palatability and Swallowability in the Development of Oral Dosage Forms for Pediatric Patient. Liza A. Squires Donald P. Lombardi Philip Sjostedt, et al. 2013: Therapeutic Innovation & Regulatory Science 47(5) 533-541

- Open the number of capsules required to make up a complete dose *[see Dosage and Administration (2.2, 2.3)]*.
- There are 4 tablets per capsule. Ensure all tablets per capsule are swallowed and no tablets are retained in the mouth.
- Swallow the tablets whole; do not cut, break, crush or chew the tablets.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action –

All of the review disciplines recommended the product for approval pending approved labeling specifying the revision to the ages for the indication. This Signatory concurs with the approval recommendation as discussed above specifying the indication of treatment of mildly to moderately active ulcerative colitis in pediatric patients 5 years and older.

13.2 Risk Benefit Assessment

I concur with the CDTL recommendation that the benefit and risk assessment supports the approval of Delzicol for the treatment of ulcerative colitis in patients ages 5-12 years with mild to moderate UC. The current formulation appears to swallowable for children with UC which has been a previously poorly managed issue for management of children with impaired swallowing function as a result of developmental maturation. The comparative bioavailability study and dissolution testing support the comparable performance of the proposed product formulation as compared to Asacol tablets. This Signatory agrees with the above assessment of PMR fulfillment but still has some outstanding concerns regarding swallowability in the youngest age child with UC. Formulation guidance on palatability assessments is critical to pediatric drug development. The EMA has published formulation guidance for the development of pediatric formulations[5]. Furthermore recent literature supports the critical investigation of palatability especially in the pediatric population. Thompson and colleagues note, "However, despite the reported importance of palatability to therapeutic adherence and compliance, there is limited scientific evidence related to the assessment of oral dosage forms, especially in the development process of pharmaceutical oral dosage forms. The VAS and facial hedonic scale are the most commonly used tools to assess palatability in pediatric populations, with no standardized assessment process or statistical analysis plan. There is a limited evidence base regarding the correlation between the palatability of oral dosage forms and treatment adherence in pediatric patients. With the growing number of compounds currently under development or reformulation for use in pediatric patients, it is advantageous for biopharmaceutical companies to consider appropriate palatability testing in the clinical development program. This assessment will assist in achieving long-term treatment adherence, resulting in improvements in overall clinical outcomes."[6]

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[5] 19 May 2011,EMA/CHMP/QWP/180157/2011,Committee for Medicinal Products for Human Use (CHMP) Guideline on Pharmaceutical Development of Medicines for Paediatric Use, Draft

[6] A Systematic Literature Review on the Assessment of Palatability and Swallowability in the Development of Oral Dosage Forms for Pediatric Patient. Liza A. Squires Donald P. Lombardi Philip Sjostedt, et al. 2013: Therapeutic Innovation & Regulatory Science 47(5) 533-541.

Deputy Director Signatory Review
Andrew E. Mulberg, MD, FAAP
September 9, 2015

This Signatory agrees that a critical component of swallowability and palatability assessment has been performed and agree with the conclusion of fulfillment of this PMR in light of proposed labeling revisions focusing on ability to open capsules and have contents swallowed which are of significantly lower diameter than any previously labeled mesalamine product. The label for the new Delzicol allows opening of a capsule to swallow individual tablets- see Section 2.3 of the PI (Important Administration Instructions. This Signatory agrees with the recommendation for an Approval action for this supplement.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
None.

Recommendation for other Postmarketing Requirements and Commitments
The outstanding PREA PMR (2011-1) (shown below) for Delzicol 400 mg delayed release capsules is considered fulfilled.

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

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/s/

ANDREW E MULBERG
09/09/2015
Deputy Director Summary Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

OFFICER/EMPLOYEE LIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 9, 2015

TO: File

THROUGH:

FROM: CAPT Kelly Richards, RN, MSN, Regulatory Project Manager

SUBJECT: Officer/Employee List

APPLICATION/DRUG: sNDA 204412/006 Delzicol (mesalamine)

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list

Andrew Mulberg
Kelly Kitchens
Kendra Worthy
Sue Chih Lee
Sushanta Chakder
Sherly Abraham
Mildred Wright
Lisa Pitt
Marjorie Dannis
Stacy Barley
Kevin Bugin
Danuta Gromek-Woods
Joette Meyer
Erica Radden
Kelly Richards
Sandhya Apparaju

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

/s/

KELLY D RICHARDS
09/09/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 1, 2015
From	Sue-Chih Lee, Ph.D. Clinical Pharmacology Team Leader CDER/OTS/OCP/DCP3
Subject	Cross-Discipline Team Leader Review
NDA#	204412/S-006
Applicant	Warner-Chilcott
Date of Submission	November 12, 2014
PDUFA Goal Date	September 11, 2015
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 in patients 5 years of age and older • Maintenance of remission of ulcerative colitis in adults
Recommended Action	*Approval*

Table of Contents

1. Introduction

This NDA supplement provides for a new formulation of Delzicol (mesalamine) delayed-release capsules 400 mg (designated by the Applicant as WC3079), which is proposed for use in patients down to 5 years of age. Note that the Applicant currently has a different formulation of Delzicol capsules 400 mg (designated as WC3045) on the market, which can only be administered to patients down to 12 years of age. The Applicant has stopped marketing Asacol (mesalamine) delayed-release tablets 400 mg but has Asacol HD (mesalamine) delayed-release tablets 800 mg on the market. These products along with their indications are listed in Table 1 below.

Table 1: Applicant's Mesalamine Products

Date of Approval	NDA	Product	Indication(s)
01/31/1992 (adults) 10/18/2013 (pediatrics)	019651	Asacol Tablets 400 mg (discontinued)	• Treatment of mildly to moderately active ulcerative colitis (UC) in patients 5 years of age and older • Maintenance of remission of UC in adults
05/29/2008 (adults)	021830	Asacol HD Tablets 800 mg	• Treatment of moderately active ulcerative colitis in adults.
02/01/2013 (adults) 04/28/2014 (pediatrics)	204412	Delzicol Capsules 400 mg (WC3045)	• Treatment of mildly to moderately active UC in patients 12 years of age and older • Maintenance of remission of UC in adults
Pending; PDUFA: 09/11/2015 (adults + pediatrics)	*The subject submission:* 204412 /S-006	*Proposed:* Delzicol Capsules 400 mg (WC3079)	*Proposed indications*: Same as the approved indications for Asacol Tablets 400 mg

The Applicant plans to withdraw Delzicol capsules 400 mg (WC3045) from the market after the current NDA supplement is approved and intends to reformulate Asacol HD to remove dibutyl phthalate from its enteric coating.

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. The dosing regimens for these products are listed in Table 2-A. 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.

Table 2-A. Approved Mesalamine Products for Adult Use

Trade Name ***Dosage form, Initial approval year***	***Induction***	***Maintenance***
Delzicol Delayed-release capsules, 2013	2.4 g/day (TID)	1.6 g/day (in 2-4 divided doses)
Apriso Extended-release capsules, 2008	-	1.5 g/day (QD)
Asacol HD® Delayed-release tablets, 2008	4.8 g/day (TID; for moderately active UC)	-
Lialda Delayed-release tablets, 2007	2.4 – 4.8 g/day (QD)	2.4 g/day (QD)
Canasa Rectal Suppository	1 g/day (QD; for ulcerative proctitis)	-
Pentasa Extended-release capsules, 1993	4g/day (QID)	-
Asacol® Delayed-release tablets, 1992	2.4 g/day (TID)	1.6 g/day (in 2-4 divided doses)
Rowasa Rectal Suspension Enema, 1987	4g (QD; for distal UC/proctitis)	-

Asacol tablets 400 mg and Delzicol capsules 400 mg (WC3045) are the only mesalamine products also approved for pediatric use to treat mildly to moderately active UC. (Note that according to the Applicant, Asacol tablets 400 mg is no longer marketed.)

Table 2-B. Dosing Regimen for mildly and moderately active UC in pediatric patients

Weight Group (kg)	Daily Dose (mg/kg/day)	Maximum Daily Dose (grams/day)
17 to <33	36 to 71	1.2
33 to <54	37 to 61	2.0
54 to 90	27 to 44	2.4

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. As such, the Applicant developed Delzicol capsules 400 mg (WC3045), which is an over-encapsulated delayed-release tablet that contains dibutyl sebacate to replace DBP as the plasticizer in the

enteric coating. Delzicol capsules (WC3045) was shown to be bioequivalent to Asacol delayed-release tablets 400 mg using criteria consistent with those described in the response letter* dated August 20, 2010, to two Citizen Petitions (FDA-2010-P-0111 and FDA-2008-P-0507) and was approved on 2/1/2013.

*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>

Specifically, the basis for approval of Delzicol (WC3045) included the following:

- Comparative PK study: The study employed a replicate design and reference-scaled BE analysis methodology was used to establish bioequivalence for three PK parameters (Cmax, $AUC_{8\text{-}48h}$ and $AUC_{0\text{-}tldc}$) as Asacol is a highly variable drug.
- Comparative dissolution testing : Testing performed using Apparatus 2 at 50 rpm to demonstrate similar dissolution characteristics in 0.1N HCl and at pH 4.5, 6.0, 6.5, 6.8, 7.0 and 7.5 when compared to those for Asacol tablets using the f2 test metric

As such, Delzicol (WC3045) received the same indications as Asacol tablets 400 mg (for adult use only at the time). Following the approval of Asacol tablets 400 mg for pediatric active, mild to moderate UC down to 5 years of age on 10/18/2013, WC3045 received an approval on 4/18/2014 for active, mild to moderate UC in patients 12 years of age and older because the capsule size was deemed inappropriate for younger patients. Consequently, the 4/18/2014 approval letter for WC3045 included a PREA requirement as shown below:

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

Therefore, the current submission is to fulfill this PREA requirement by developing a formulation suitable for patients down to 5 years of age.

2.2 Current Submission

In this NDA supplement, the Applicant is pursuing the approval of a proposed formulation, Delzicol delayed-release capsules 400 mg (WC3079). Each capsule contains four 100 mg mesalamine delayed-release tablets. To support the approval of this supplemental application, the Applicant provided the following data:

- CMC information for the proposed formulation
- A relative bioavailability study (PR-07513) to evaluate the PK profile, food effect, and bioavailability of the proposed Delzicol capsules 400 mg (WC3079) relative to the reference product, Asacol tablets 400 mg.
- A study (PR-00514) in healthy children (5-11 years old) to characterize the swallowability of WC3079.
- Comparative dissolution studies for Delzicol capsules (WC3079 vs. WC3045)
- In vitro alcohol dose dumping studies on WC3079 (proposed Delzicol), WC3045 (approved Delzicol), and Asacol.

No safety and efficacy trials were conducted by the Applicant using the proposed capsule product. The proposed indications and dosing regimens are the same as those for Asacol tablets 400 mg.

As with the original NDA for Delzicol (WC3045), there are special features in the comparative PK and dissolution 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. Specifically, the comparative PK study involves one additional metric (i.e. partial AUC: $AUC_{8\text{-}48h}$) and dissolution testing includes media of a series of pH's as described in Section 2.1.2, 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 certain disciplines refer to the proposed capsule formulation as WC3079 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 Panorama (Biopharm and CMC reviews) or DARRTS (all other reviews).

- Clinical Pharmacology Review by Sandhya Apparaju/ Sue-Chih Lee, dated August 12, 2015
- Biopharm Review by Vincent (Peng) Duan/Kelly Kitchens dated August 5, 2015
- CMC Review by Libaniel Rodriguez/Thomas Oliver, dated August 24, 2015
- Clinical Review by Marjorie Dannis/ Anil Rajpal, dated August 5, 2015
- Nonclinical Review by Sushanta Chakder dated August 5, 2015
- Biostat Consult Review by Zhuang Miao/Meiyu Shen/Yi Tsong dated August 3, 2015
- DPHM (PMHS) review (re: labeling & PREA requirements) by Erica Radden/Hari Sachs/Linda Lewis, dated August 12, 2015
- OPDP Labeling Review Memo by Meeta Patel, dated July 28, 2015
- DMEPA labeling review by Sherly Abraham/ Kendra Worthy, dated May 19, 2015
- OSI Memo by Shila Nkah, dated April 9, 2015

3. OPQ Reviews - CMC and Biopharm

(A) CMC REVIEW

No deficiencies are cited in the CMC review. The reader is referred to the CMC Review by Dr. Libaniel Rodriguez dated August 24, 2015 (Panorama) or August 27, 2015 (DARRTS) for complete information.

- *Drug Product:* Each proposed WC3079 capsule contains four 100-mg mesalamine delayed-release tablets rather than one 400-mg tablet in each WC3045 capsule. There are no changes to the drug substance, excipients, capsule shell material, analytical testing or container closure compared to those for the manufacture of the approved Delzicol capsules (WC3045). The manufacturing process has only minor modifications.

  Tablet Core: The tablet core for the proposed Delzicol capsules (WC3079) has the same components and composition as those for the approved Delzicol capsules (WC3045), which are also the same as those for Asacol Tablets.

  Tablet Coat: The components for tablet coating for the proposed WC3079 capsules remain the same as those for WC3045 but the composition differs to accommodate the change in surface area for four 100-mg tablets as opposed to one 400-mg tablet in WC3045.

  Capsule Shell: The capsule shells for WC3045 and WC3079 differ in color and ink imprint. The WC3045 capsules is manufactured with a red size (b) (4) capsule imprinted in white ink and the proposed WC3079 capsules is manufactured with a clear size (b) (4) capsule imprinted in black ink.

  Container Closure: The proposed Delzicol capsules (WC3079) are packaged in a 180 count (trade) presentation and a 12 count (sample) presentation. The 180 count container closure system is a (b) (4) bottle with a (b) (4) child resistant closure containing a foil inner seal. This presentation contains (b) (4) desiccants (b) (4)g in total). The 12 count container closure system is a (b) (4) bottle with a (b) (4) child resistant closure containing a foil inner seal. This presentation contains cotton and (b) (4) desiccants (b) (4)g in total).

  Manufacturing, Packaging and Testing: The sites responsible for the manufacture, packaging and testing of the proposed Delzicol capsules (WC3079) are the same as those for the approved Delzicol capsules (WC 3045).

  Specifications: Same as the approved Delzicol capsules with the exception of Appearance description to accommodate the different color capsule with ink imprint.

  Stability: The Applicant provided six months of ICH long term and accelerated stability data from three batches of the proposed capsules (WC 3079) packaged in the 180 count and 12 count configurations, which showed the results remained within acceptance criteria for the tested conditions. No specific trends were observed for any of the parameters tested.

  Expiry dating: Based on the stability data available to date, Warner Chilcott proposes a 24 month shelf life for the proposed product. Dr. Rodriguez commented that the data presented in together with historical data from the currently approved Delzicol capsules form the basis for allowing a 24 months shelf life for the proposed drug product. The 24 months shelf life for the proposed capsules is therefore granted.

  Manufacturing sites: On May 12, 2015, the Office of Process and Facilities (OPF) recommended the manufacturing site(s) for approval.

Components and Composition: The components and composition for the proposed Delzicol capsules (WC3079) are shown in Table 3-A (b) (4) and Table 3-B (b) (4) (b) (4)

Table 3-A. Components and Composition of the proposed Delzicol capsules (WC3079)

Component	Quality Standard	Function	Quantity		
			mg/tablet	mg/capsule	% w/w (capsule)
(b) (4)					
Mesalamine	USP	Active ingredient	100.0	400.0	(b) (4)
Lactose monohydrate	NF	(b) (4)			
Povidone	USP				
Sodium starch glycolate	NF				
Magnesium stearate	NF				
Talc	USP				
Colloidal silicon dioxide	NF				
(b) (4)	USP				
		Subtotal	(b) (4)		
(b) (4)					

Table 3-B: (b) (4)

Component	Quality Standard	Function	Quantity		
			mg/tablet	mg/capsule	% w/w (capsule)
(b) (4)					
Eudragit S (b) (4)	-	(b) (4)			
Talc	USP				
Dibutyl sebacate	NF				
Ferric oxide, red	NF				
Ferric oxide, yellow	NF				
(b) (4)	NF				
	USP				
(b) (4)					
Polyethylene glycol (b) (4)	NF	(b) (4)			
(b) (4)	USP				
(b) (4)					
Hydroxypropyl methylcellulose (HPMC) (b) (4)	-	(b) (4)			
Total Theoretical Capsule Weight			-	**671**	**100**
					(b) (4)

(B) BIOPHARM REVIEW

Dr. Duan reviewed the in vitro dissolution and in vitro alcohol dose dumping studies. Although the proposed Delzicol capsules did not pass the f2 test for dissolution at pH 6.5, this is not of concern because examination of the individual dissolution data indicated that there were less outliers for the proposed Delzicol product compared to the reference product (Asacol tablets) as the product is designed to release drug at a target pH of 7. The in vitro alcohol dose dumping studies did not raise a safety concern. The reader is referred to the reviews by Dr. Peng Duan in Panorama dated August 5, 2015, for more details.

Comparative Dissolution Testing - as part of bioequivalence/relative bioavailability assessment:

The Applicant conducted two comparative dissolution studies:

Study 1:
Dissolution of Asacol tablets, the proposed Delzicol capsules (WC3079) and individual 100 mg tablets from WC3079 capsules were tested using the USP dissolution apparatus II. Dissolution media included 0.1N HCl and buffer solutions at pH 6.0, 6.5, 6.8, 7.2 and 7.5. Multipoint dissolution profile comparisons were made as shown in Table 4. The similarity factors (f2) values were calculated. In principle, the f2 test does not apply when the variability (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. As the dissolution testing did not follow the guidance, this study is considered supportive.

Study 1 Results:

- *Proposed Delzicol capsule vs. Asacol tablet:* Dissolution passed the f2 test (i.e., f2 > 50) at pH 6.5, 7.2 and 7.5 but not at pH 6.8 as shown in Table 4 while dissolution was negligible in 0.1N HCl and at pH 6.0.

Table 4: Dissolution Similarity – Proposed Delzicol Capsules vs. Asacol Tablets (Study 1)

Evaluation Stage	f2 Value (from Applicant)	Bootstrap f2 mean with lower 90% bound
pH 6.5 Phosphate buffer	72	72.8 (54.9)
pH 6.8 Phosphate buffer	50	**51.0 (42.2)**
pH 7.2 Phosphate buffer	60	71.3 (61.9)
pH 7.5 Phosphate buffer	58	66.6 (56.6)

- *Single 100-mg tablet vs. Asacol Tablets:* The f2 test failed at pH 6.8, 7.2 and 7.5. This is not considered critical because the minimum dose is 400 mg.

Study 2: *Two-Stage dissolution testing*: A study was conducted to test the dissolution of WC3079 capsules, WC3079 without capsule shell (i.e., four 100-mg tablets), WC3079 single 100-mg tablet, and Asacol 400 mg tablets per the September 2012 FDA draft guidance on demonstration of bioequivalence for mesalamine delayed release tablets. The method for the 2-stage dissolution test method is shown in Table 5. Because the variability was very high, Dr. Duan conducted bootstrapping to estimate the f2 values.

Table 5: Dissolution Test Method for Study 2

Parameter	Description
Dissolution Apparatus	USP Dissolution Apparatus II, Paddles, (Vankel-VK7000, or equivalent)
Temperature	37°C ± 0.5°C
Sample Size	n=12
Pretreatment Stage	500 mL of 0.1N HCl
Evaluation Stage	900 mL of pH 4.5 Buffer 900 mL of pH 6.0 Buffer 900 mL of pH 6.5 Phosphate buffer 900 mL of pH 6.8 Phosphate buffer 900 mL of pH 7.2 Phosphate buffer 900 mL of pH 7.5 Phosphate buffer
Paddle Speed	Pretreatment Stage: 100 rpm Evaluation Stage: 50 rpm
Sampling Times	0.1N HCl Pretreatment Stage: 120 minutes pH 4.5, pH 6.0, pH 6.5, pH 6.8, pH 7.2 and pH 7.5 evaluation Stage: 0, 10, 20, 30, 45, 60, 75, 90, 120 and 150 minutes

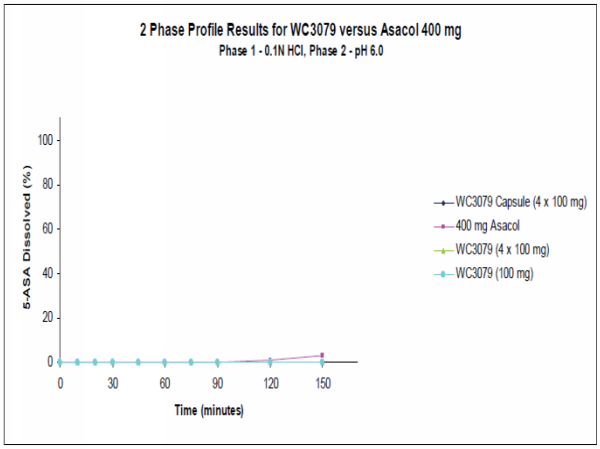
Study 2 Results:

- *Proposed Delzicol capsule vs. Asacol tablet: The f2 tests passed at all pH values except for* pH 6.5, where the f2 value was estimated to be 61 by the Applicant and 62.6 by Dr. Duan from bootstrapping with the lower limit of 90% CI being 44.3% (<50%). (See Table 6 and Figure 1.)

Table 6: Dissolution Similarity - Proposed Delzicol Capsules vs. Asacol Tablets (Study 2)

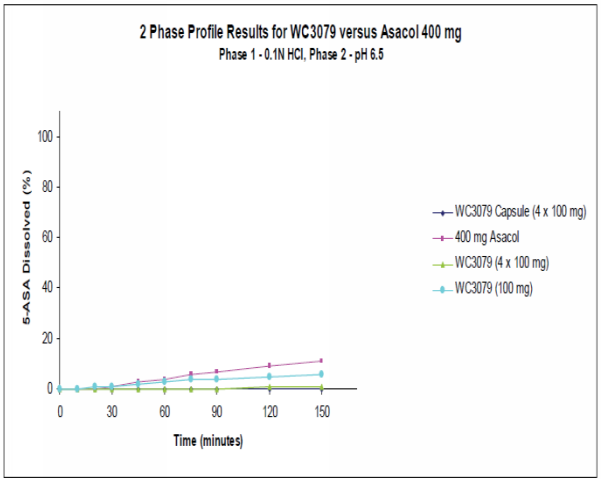
Evaluation Stage	f2 Value (calculated by the Applicant)	f2 (bootstrap analysis with 90% lower bound)
pH 4.5 Acetate buffer	100	N/A
pH 6.0 Phosphate buffer	92	N/A
pH 6.5 Phosphate buffer	61	**62.6 (44.3)**
pH 6.8 Phosphate buffer	84	84.3 (72.3)
pH 7.2 Phosphate buffer	63	67.3 (58.3)
pH 7.5 Phosphate buffer	79	88.2 (79.9)

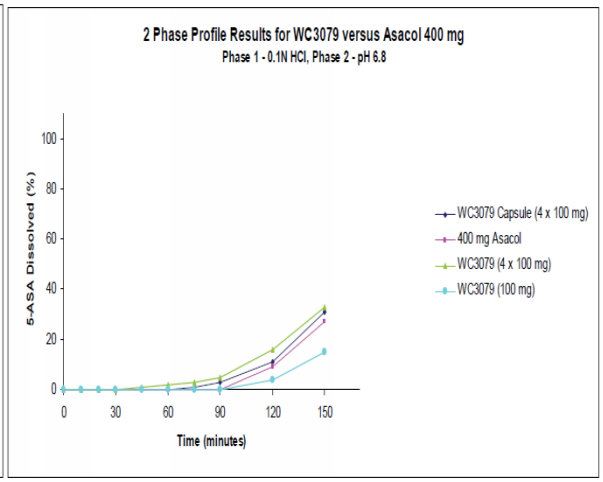
Figure 1. Mean Dissolution Profiles for Asacol® Tablets 400mg (red), WC3079 Capsules (black), WC3079 4x 100-mg Tablets (green) and WC3079 single 100-mg Tablet (blue) at pH 6.0, 6.5, 6.8, 7.2 and 7.5

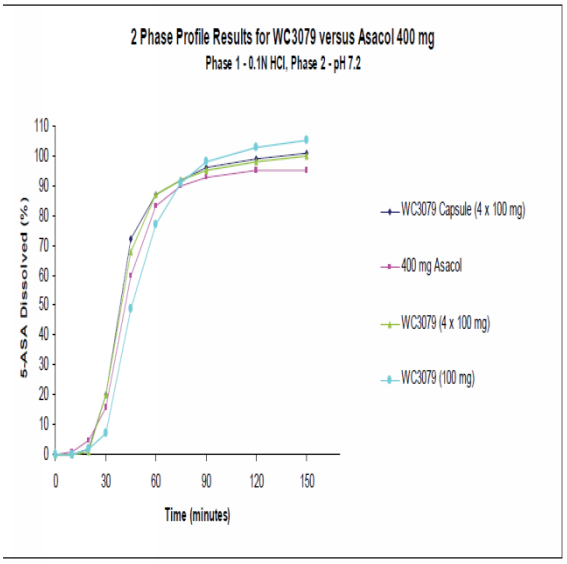


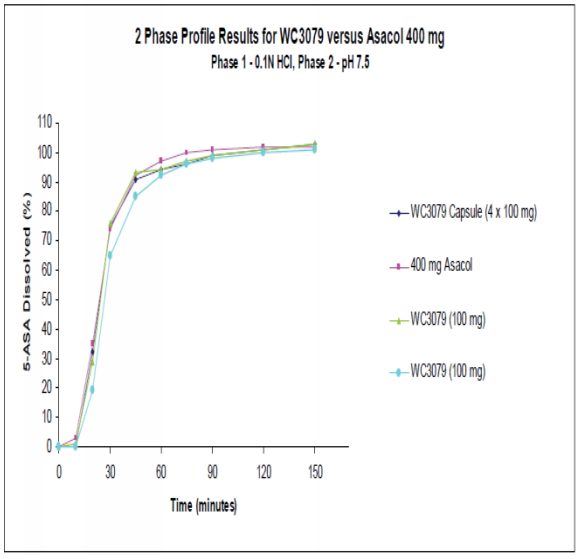
pH of dissolution test media in Figure 1:

Left Panels	***Right Panels***
Top : 6.0	-
Middle: 6.5	6.8
Bottom: 7.2	7.5









- *Proposed Delzicol capsule without capsule shell vs. Asacol tablet: The f2 tests passed at all pH values except for* pH 6.8, where the f2 value was estimated to be 68 by the Applicant and 69.3 by Dr. Duan from bootstrapping with the lower limit of 90% CI being 47.2% (<50%). (See Table 7 and Figure 1.)

Table 7: Dissolution Similarity – Proposed Delzicol Capsules without capsule shell versus Asacol Tablets (Study 2)

Evaluation Stage	f2 Value	f2 (bootstrap analysis with 90% lower
pH 4.5	100	N/A
pH 6.0	92	N/A
pH 6.5	78	79.5 (52.3)
pH 6.8	68	**69.3 (47.2)**
pH 7.2	60	65.3 (51.7)
pH 7.5	52	59.9 (51.5)

In Study 2, the f2 test did not have robust results at pH 6.5 for the proposed Delzicol capsules and at pH 6.8 for the capsule formulation without the capsule shell. In both scenarios, the mean f2 value from bootstrapping was above 60 while the lower limit of the 90% CI was <50% (~45%). Individual dissolution data exhibited high variability, therefore, the sample size (12 units) may prevent a precise estimate of the mean value. As drug release at these pH values were low, the differences are considered unlikely to have a significant clinical impact. (b) (4)

[redacted]

Dissolution Specifications for batch release and stability testing

The sponsor proposed the dissolution test method and specifications as described below. Based on the data for batch release and stability batches, Dr. Duan found these specifications acceptable.

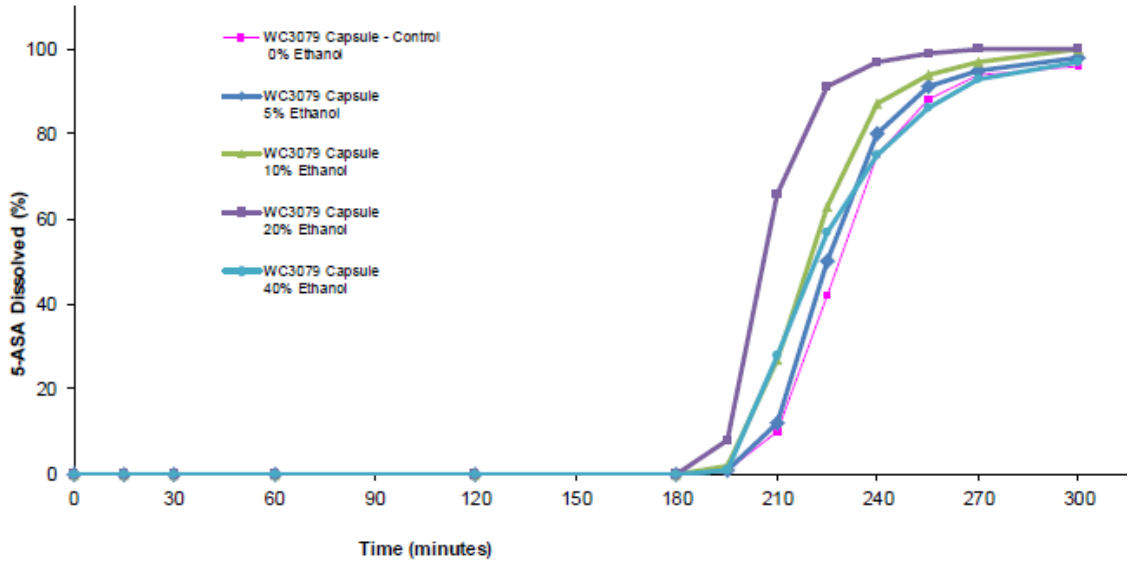
- Stage 1: 0.1N HCl (Type II Paddle 100 RPM, 2 hrs)
  Level 1: No individual value exceeds 1% dissolved
  Level 2: Average of the 12 units (L1 + L2) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved.
  Level 3: Average of the 24 units (L1 + L2 + L3) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved
- Stage 2: pH 6.0 (Type II Paddle 100 RPM, 1 hr)
  Level 1: No individual value exceeds 1% dissolved
  Level 2: Average of the 12 units (L1 + L2) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved
  Level 3: Average of the 24 units (L1 + L2 + L3) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved
- Stage 3: pH 7.2, Q=80% (Type II Paddle 50 RPM, 1.5 hrs)
  Level 1: Each unit is not less than 85% (Q+5%)

Level 2: Average of the 12 units (L1 + L2) is equal to or greater than 80% (Q), and no unit is less than 65% (Q-15%).
Level 3: Average of the 24 units (L1 + L2 + L3) is equal to or greater than 80% (Q), and not more than two units are less than 65% (Q-15%) and no unit is less than 55% (Q-25%).

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:

The Applicant conducted the alcohol dose dumping study to evaluate the drug release of WC3079 capsules and WC3079 1x100 mg single coated tablet as well as WC3045 capsules in the presence of various concentrations of alcohol up to 40%. All scenarios had no drug release in 0.1 N HCl and pH 6.0 buffer stage, in the presence of up to 40% of alcohol. At pH 7.2, a somewhat faster dissolution was shown in the presence of alcohol, especially at 20% (Figure 2). Because the delayed release characteristics have not been compromised as demonstrated by zero drug release during Acid Stage and at pH 6.0 Buffer stage, the dissolution findings at pH 7.2 does not raise particular safety concerns.

Figure 2: Comparative dissolution profiles for the proposed Delzicol capsules at pH 7.2 in the presence of various alcohol concentrations (0%, 5%, 10%, 20% and 40%)



3.1 Final Recommendation

This NDA is recommended for approval from a CMC perspective. There are no outstanding issues with drug substance and drug product.

4. Nonclinical Pharmacology/Toxicology

The reader is referred to the review by Dr. Sushanta Chakder dated August 5, 2015, for more details.

No new nonclinical pharmacology/toxicology information is provided by the Applicant to support this application. However, the Nonclinical Pharmacology/Toxicology Review has the following labeling recommendations:

- Section 8.1 Pregnancy: To add a risk summary regarding negative findings in animal studies and cautionary language about overall insufficient data to inform risk
- Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: To include information regarding negative findings in animal studies and in Ames assay
- Section 13.2 Animal Toxicology and/or Pharmacology: to include renal toxicity findings in animal studies.

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/Sue-Chih Lee dated August 12, 2015, for further details.

Overview: To support the proposed Delzicol capsule formulation (WC3079), the Applicant conducted a study entitled "A Study to Assess the Relative Bioavailability and the Effect of Food of a New Delayed-Release Mesalamine Formulation (WC3079-19F) in Healthy Volunteers, Study PR-07513." The study demonstrates that the bioavailability of the proposed capsule formulation is comparable to the reference product (Asacol Tablets) under the conditions studied (fasting). Regarding food effect, a high fat meal increased the mesalamine systemic exposure by approximately 30-45% following administration of the proposed product. This is similar to what was observed for the approved Delzicol Capsules (WC3045). Therefore, the proposed product can be administered without regard to food.

Study PR-07513: This was an open-label, randomized, single-dose, replicate treatment, 5-period, 4-sequence, 2-formulation crossover study in 160 healthy male and female subjects to assess (1) the bioavailability of the proposed formulation (WC 3079; Test product) relative to Asacol DR tablets 400 mg (Reference product) under fasting conditions and (2) the effect of food on the bioavailability of the proposed Delzicol capsules (WC3079). Treatment periods were separated by at least 7 days. Subjects were randomly assigned to one of the following 4 treatment sequences:

Sequence A: RFTRT; Sequence B: TRTFR; Sequence C: RTFRT; Sequence D: TRFTR, where R represents the reference product (Asacol), T is the test product (proposed Delzicol WC3079) and F is fed conditions for the test product. For the fed conditions, subjects were given a high fat meal 30 minutes prior to dosing. Assay of plasma mesalamine concentrations (LLOQ: 2 ng/mL) was performed by (b) (4).

Relative Bioavailability Data Analysis Methodology: The metrics for comparison included Cmax, AUC0-tldc and AUC8-48h. The partial AUC (AUC8-48h) was recommended by the Agency as was used in previous approval of Delzicol capsules 400 mg (WC3045). 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. (Please refer to the OGD Draft BE Guidance on Progesterone for the analysis.) Bioequivalence criteria for the PK metrics are:

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

and

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

- $\bar{Y}_T$ 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:

In this study, 146 subjects completed the study. Mean plasma concentration-time profiles for the test and reference mesalamine formulations are shown in Figure 1. Arithmetic and geometric mean PK parameter values for test and reference product are given in Table 8.

Table 8: Arithmetic Mean (SD) and Geometric Mean PK Parameters (N=146)

Arithmetic Mean (SD) Geometric Mean	**C_{max} (ng/mL)**	**AUC_{8-48h} (ng.h/mL)**	**AUC_{tldc} (ng.h/mL)**	**Tlag (h)**	**Tmax (h) Mean/Median**
Reference R1	159 (337) 55.4	882 (803) 453	1083 (1021) 531	8.1 (4.7)	17.6 (12.7)
Reference R2	157 (286) 63.6	889 (670) 352	1144 (955) 644	7.7 (4.8)	16.6 (11.7)
Test T1	207 (323) 78.6	701 (620) 487	1035 (987) 667	6.2 (4.3)	13.6 (11.5)
Test T2	201 (422) 60.6	712 (866) 445	1007 (1222) 574	6.8 (4.3)	15.4 (13.0)
Test with food, F	214 (320) 90.8	948 (853) 679	1128 (974) 780	9.9 (4.1)	17.6 (11.1)

Data Analysis:

Relative bioavailability: In the data analysis, the Applicant eliminated treatments that were not relevant to the particular analysis of interest and renumbered the study periods. This data handling assumed absence of period effects. The sponsor concluded that all PK parameters (Cmax, AUC8-48h, & AUC0-tld) met the BE criteria using the reference-scaled BE methodology for PK data (Table 9).

Table 9. Sponsor's Analysis Results on Bioavailability of the Proposed Delzicol Capsules (WC3079) versus Asacol Tablets

		Within-Subject SD (%CV)		Geometric Mean (LSM)		Ratio (%)	95% Upper Bound of the Linearized
PK Parameter	N	Test	Reference	Test	Reference	(T / R)	Criterion
Cmax	146	1.20 (179)	1.31 (214)	68.9	59.4	115.96	-1.11
AUC8-48	146	0.739 (85.2)	1.52 (301)	465	484	96.07	-1.54
AUC0-tldc	146	0.833 (100)	1.52 (301)	618	586	105.52	-1.53

As the study design is unusual, the Office of Biostatistics (OB/DBVI) was consulted on data analysis. DBVI concluded that the study design and data features render it impossible to apply appropriate statistical methods to assess the relative bioavailability. Additionally, question was raised that some subjects had very low concentrations and exclusion of those data can impact the analysis outcome. Please refer to the review by Dr. Zhuang Miao dated August 3, 2015.

As such, the Clinical Pharmacology Review Team examined various aspects of the study and conducted further analyses of the data.

Inspection of the individual subject data by the Clinical Pharmacology Review team revealed that subjects with no or low systemic exposure should not be excluded from the analyses because most subjects with zero exposure in one study period had high concentrations when the same dosage form was given in another period (Table 10). As such, the low concentrations should be treated as part of the PK variability and should be included in the analysis.

Table 10: Subjects with zero concentrations*

ID	**R1** AUC_{8-48}	**R2** AUC_{8-48}	**T1** AUC_{8-48}	**T2** AUC_{8-48}
(b) (6)	1	5 1	936 4	801 2
	1	1134	158	59.3
	1	275	365	1018
	1	223	604.4	195.5
	1	623	557	405
	1	684	260	445
	1	825	1077	450
	1	812	369	12.8
	1	1147	326	1416
	30.2	1	213	156
	958	1	162	416
	456	1	572	289
	791	1	16.3	213

(b) (6)				
	422	1	69	206
	691	1	2	1
	969	387	1	43

*Zero concentrations are given a value of 1

One additional analysis used PK data from fasted periods for Sequences #C & D as both of these sequences had the fed treatment on the same study period (i.e., Period 3). The analysis showed that all PK parameters met the BE criteria using the reference-scaled BE testing (Table 11).

Table 11: Reviewer's Analysis of data from Sequences C and D

Parameter	T/R Ratio	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
$LAUC_{TLDC}$	0.92	2.6431803	1.6257861	-1.636809	Scaled/PE	PASS
$LAUC_{8-48}$	0.87	2.6813033	1.6374686	-1.642708	Scaled/PE	PASS
LCMAX	0.97	1.8334341	1.3540436	-1.142678	Scaled/PE	PASS

Conclusion: The Clinical Pharmacology Review Team met with Dr. Hae-Young Ahn, Deputy Director of Division of Clinical Pharmacology III, to discuss path forward. As the washout period was sufficient to avoid drug concentration carryover, Dr. Ahn considered that the assumption of no period effect is reasonable while dismissing the whole dataset is not. The Clinical Pharmacology Review Team concluded that the bioavailability of the proposed Delzicol Capsules 400 mg (WC3079) is comparable to that for the Asacol Tablets 400mg. However, the proposed product is not considered bioequivalent to the reference product and the label will not state interchangeability between the proposed Delzicol (WC3079) and the approved Delzicol product (WC3045) since the dissolution testing did not show robust similarity and the bioavailability analysis involves the assumption of no period effect even though that is considered a reasonable assumption. For future studies, it is important that the Applicant adhere to the balanced, fully or partially replicated study designs to avoid the above statistical issues.

Food effect:

Using parameter estimate presented in Table 8, a high fat meal increased the mesalamine systemic exposure by approximately 30-45% (Table 12). This is similar to what was observed for the approved Delzicol Capsules (WC3045). As such, the proposed product can be administered without regard to food.

Table 12. Impact of concomitant high fat meal

		Within-Subject SD (CV%)		Geometric Mean (LSM)		Ratio (%)	95% Upper Bound of the Linearized
PK Parameter	N	Test	Reference	Test	Reference	(T / R)	Criterion
Cmax	146	NA	1.20 (179)	91.1	69.0	132.11	-0.825
AUC8-48	146	NA	0.738 (85.1)	681	466	146.22	-0.152
AUC0-tldc	146	NA	0.831 (99.7)	802	620	129.39	-0.354
AUC0-inf	99	NA	0.575 (62.6)	1227	1087	112.90	-0.183

Cmax = Maximum plasma concentration (ng/mL);
AUC8-48 = AUC from time 8 hours to 48 hours (ng·h/mL);
AUC0–tldc = AUC from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)
Test(T) = WC3079 capsule with food; Reference(R) = WC3079 capsule fasted.
Ratio = The ratio of geometric means. NA = not applicable
BE = Bioequivalence; SD = standard deviation; CV%=100*sqrt(exp(SD**2)-1); LSM = least squares mean from ANOVA model

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 an oral product and is not an antimicrobial agent.

7. Clinical – Efficacy and Safety

The reader is referred to the review by Dr. Majorie Dannis dated August 5, 2015 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 that the proposed product is comparable in in vivo performance to the reference product, Asacol tablets 400 mg. Note that as with the approved Delzicol capsules (WC3045), the proposed Delzicol capsules are also phthalate-free. As requested by the Agency during a Type c meeting held on January 15, 2013, the Applicant conducted a swallowability study in healthy children.

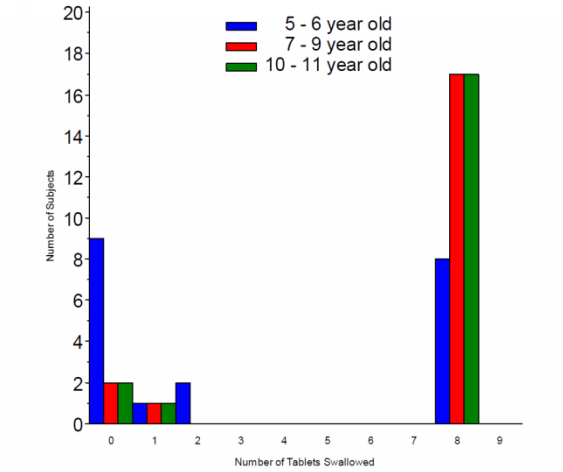
Study PR-00514 (Swallowability Study)

Study PR-00514 was a single-center, open-label, single-dose study conducted in 60 healthy children aged 5 to 11 years to characterize the swallowability of placebo tablets contained in WC3079 capsules in these children. All subjects were asked to swallow 8 placebo tablets as contained in two WC3079 placebo capsules. All 60 healthy children (30 females and 30 males) completed the study.

Results: Overall, 42 (70%) of the children swallowed all 8 tablets.

- 7 -11 years olds: 85% (34/40) swallowed 8 tablets
  10% (4/40) swallowed 0 tablets (2 patients swallowed 1 tablet)
- 5- 6 year olds: 40% (8/20) swallowed 8 tablets
  45% (9/20) swallowed 0 tablets
  (1 patient swallowed 1 tablet; 2 patients swallowed 2)
- Most children swallowed the tablets in < 5 minutes
  - 3 children swallowed 1 additional tablet between 5 and 10 minutes after administration

Figure 3: Number of tablets Swallowed in **Study PR-00514 by age group**



Although a significant number of healthy children did not swallow any tablets, data from the literature suggest that training on pill swallowing can be used for patients with chronic diseases. The size of the 100 mg tablets (inside the capsule) is clearly smaller than the Asacol 400 mg tablet which is currently approved in patients down to 5 years of age. The ability of children to take this pediatric formulation can be further assessed in a future pediatric maintenance trial.

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 comparable bioavailability between the proposed product and the reference Asacol Tablets.

7.3 Review Summary - Safety

A review of safety data from Study PR-00514 and PR-07513 revealed no new or unexpected adverse events. Current adverse event labeling for ADelzicol400 mg delayed release tablets appears adequate and can be relied upon for the labeling of the proposed product.

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 reader is referred to the review by Dr. Erica Radden dated August 12, 2015.

As stated in Sections 2.1.2 and 2.2, the current submission is to fulfill a PREA requirement (2011-1) by developing a formulation suitable for patients down to 5 years of age, which was triggered by the approval of the Delzicol Capsules (WC3045).

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

Instead of conducting a study in pediatric patients, the Applicant submitted four studies to support the approval of the proposed Delzicol capsules (WC3079) by bridging to Asacol tablets. The relative bioavailability study and dissolution testing support the comparable performance of the proposed product as compared to Asacol tablets. The swallowability study results are inconclusive but the size of the individual tablets in the proposed capsules are obviously smaller than the Asacol tablets (Figure 4). As such, the PREA requirement 2011-1 is considered fulfilled.

Figure 4. Size of the Applicant's Mesalamine Products

- Asacol tablet 400 mg ((b) (4) mm)
- Delzicol capsule 400 mg (WC3045; size (b) (4) capsule, (b) (4) mm)
- The proposed Delzicol 400 mg capsuls (WC3079; size (b) (4) capsule, with 4 x100 mg tablets [(b) (4) mm diameter/ (b) (4) mm thickness])

The Applicant still has another PREA requirement (2011-2) to fulfill:

> **"2011-2** A randomized, double-blind study in pediatric patients ages 5 to 17 years using an age-appropriate formulation for the maintenance of remission of ulcerative colitis."

The current submission does not trigger PREA as there is no new indication, route of administration, dosage form, dosing regimen, or active ingredient.

10. Other Relevant Regulatory Issues

10.1 Office of Scientific Investigations (OSI) audits

The reader is referred to the memo by Dr. Shila Nkah dated April 9, 2015, and the OSI Inspection request by Dr. Sandhya Apparaju dated January 9, 2015, for further information. The overall conclusion is that the bioequivalence data are acceptable for review.

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

- *Clinical sites:* QPS Bio-Kinetic, Address: 1820 West Mount Vernon, Springfield, MO 65802.
- *Analytical site:* (b) (4)

OSIS recommended in their memo dated April 9, 2015, to accept data without an on-site inspection based on recent inspection finding at QPS Bio-Kinetic, which was classified as No Action Indicated (NAI).

10.2 QT Prolongation Potential

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

11. Labeling

11.1 Proprietary name

This submission is for a new formulation; no new proprietary name is needed.

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

OPDP had no additional comments based on a memo from Meeta Patel dated July 28, 2015.

11.3 Physician Labeling / Medication Guide / Carton and Container Labeling

DMEPA

For DMEPA comments, the reader is referred to the review by Dr. Sherly Abraham dated May 19, 2015, for complete information.

Recommendation regarding Prescribing information:

- Consider replacing the symbols "<" and "≥" with their intended meanings in in the pediatric table in Dosing and Administration to prevent misinterpretation and confusion.
- The dose in the same pediatric table in Dosing and Administration contains a trailing zero. Remove the trailing zero (e.g. 2 g) to avoid a ten-fold misinterpretation.

Recommendation regarding container label:

- Since this is a unique formulation, i.e., a capsule that contains four tablets, it is important for patients and caregivers to clearly understand the important administration instructions. Therefore, move the important warning statements, "Swallow the capsules or tablets whole; do not cut, break, crush or chew the capsule or the tablet. The capsule may be carefully opened and the contents (tablets) can be swallowed." to the principle display panel under the strength presentation.

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
- CDTL Recommendation for Regulatory Action: Approval

12.2 Risk Benefit Assessment

The risk benefit was assessed in the review by Dr. Majorie Dannis dated August 5, 2015. The proposed product can be used in patients down to 5 years of age and does not contain dibutyl phthalate in its enteric coating while it will have comparable in vivo performance in terms of efficacy compared to the reference product (Asacol tablets). Therefore, the benefit of the proposed product is expected to outweigh the risk.

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 current submission does not trigger PREA as there is no new indication, route of administration, dosage form, dosing regimen, or active ingredient. However, there is a pending PREA requirement "2011-2: A randomized, double-blind study in pediatric patients ages 5 to 17 years using an age-appropriate formulation for the maintenance of remission of ulcerative colitis."

12.5 Recommendation for other Postmarketing Study Requirements (PMRs)

None

12.6 Recommendation for Postmarketing Study Commitments (PMCs)

None

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/s/

SUE CHIH H LEE
09/03/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

MEDICAL REVIEW(S)

CLINICAL REVIEW

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

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

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

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

1.2 Risk Benefit Assessment

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

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

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

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

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

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

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

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

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

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarketing Requirements and Commitments

None

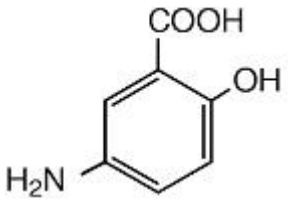
[1] Meltzer et al, 2006

2 Introduction and Regulatory Background

2.1 Product Information

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

Structural formula:

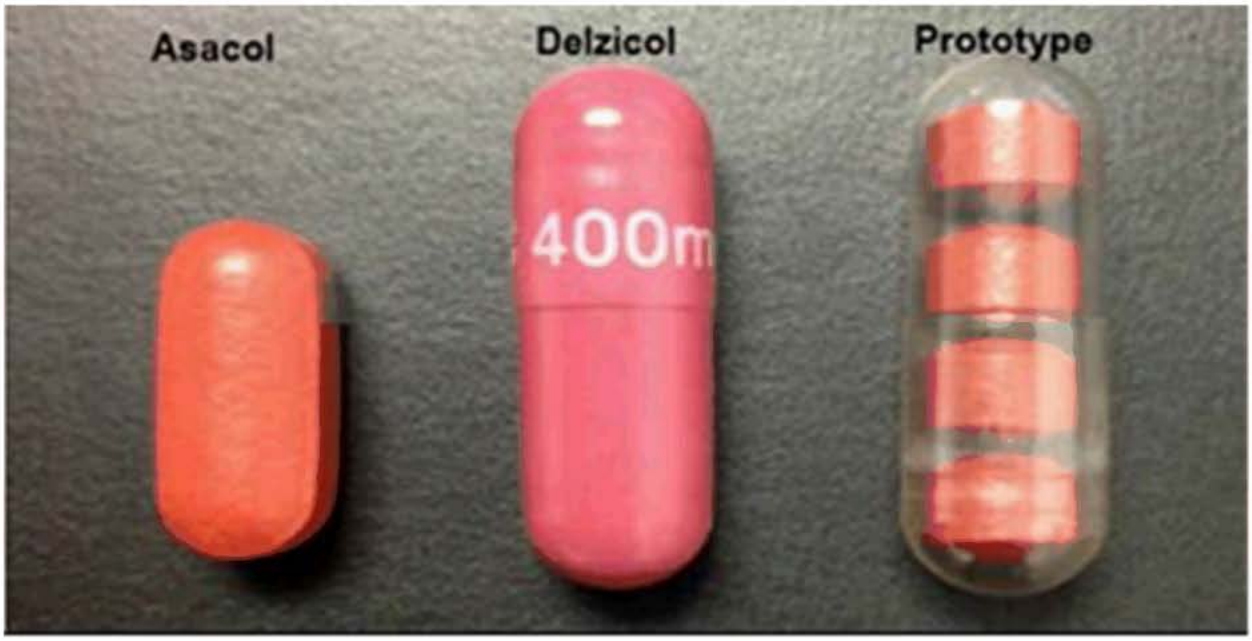


Therapeutic Class:	Aminosalicylate
Formulation:	Delayed-release capsules containing four 100 mg mesalamine delayed release tablets
Proposed indication:	Treatment of mildly to moderately active ulcerative colitis

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

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

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



2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Products to Treat Ulcerative Colitis

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

* up to 3 months

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2. Pre-submission Regulatory History, NDA 204412

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

2.6 Other Relevant Background Information

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

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

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

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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

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4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

Mesalamine is thought to exert its pharmacologic effects topically on the GI tract. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways (i.e., prostanoids), and through the lipoxygenase pathways (i.e., leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs)), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

4.4.3 Pharmacokinetics

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

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

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Clinical studies Submitted for NDA 204412

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

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Study 00514 (Swallowability Study)

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

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

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

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

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

Study PR-07513 (Relative Bioavailability Study)

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

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

Subjects were randomly assigned to one of four treatment sequences:

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

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

5.2 Review Strategy

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

5.3 Discussion of Individual Studies/Clinical Trials

Study PR-00514 (Swallowability Study)

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

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

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

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

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

Study Population

Inclusion Criteria

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

Exclusion Criteria

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

Treatments Administered

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

Selection of Doses in the Study

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

Disposition of Subjects

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

Demographic and Other Baseline Characteristics

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

Table 4: Summary of Demographic and Other Baseline Characteristics

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

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Swallowability Results

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

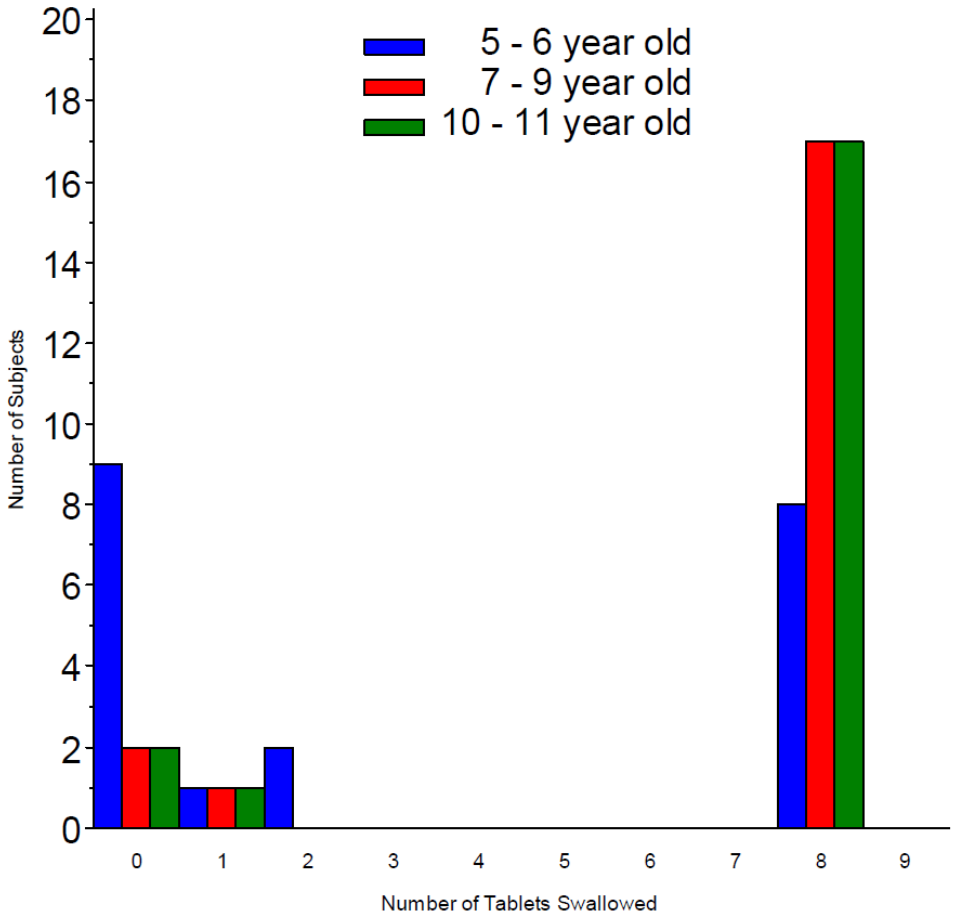
- 45% (9/20) swallowed 0 tablets
- (1 patient swallowed 1 tablet; 2 patients swallowed 2)

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

Swallowability by Age

Figure 2 below displays the results by in graphic format.

Figure 2: Swallowability by Age



Electronically copied and reproduced from CSR, pg 18 Fig 1

Discussion

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

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

6 Review of Efficacy

Efficacy Summary

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

6.1 Indication

Proposed indication:

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

6.1.1 Methods

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

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

[2] Meltzer et al, 2006

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

6.1.2 Demographics

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

6.1.3 Subject Disposition

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

6.1.4 Analysis of Primary Endpoint(s)

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

6.1.5 Analysis of Secondary Endpoints(s)

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

6.1.6 Other Endpoints

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

6.1.7 Subpopulations

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

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

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

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No efficacy studies were submitted in support of this application.

6.1.10 Additional Efficacy Issues/Analyses

No efficacy trials were submitted in support of this application.

7 Review of Safety

Safety Summary

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

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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

7.1.2 Categorization of Adverse Events

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

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

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

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

7.2 Adequacy of Safety Assessments

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

Table 5. Study Flow Chart, Study PR-07513

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

ECG= electrocardiogram; PK = pharmacokinetic

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

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

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

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

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

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

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

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

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

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

7.2.2 Explorations for Dose Response

There was no exploration for dose response.

7.2.3 Special Animal and/or In Vitro Testing

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

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

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

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

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

7.3 Major Safety Results

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

Table 6. Summary of Safety Results

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

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

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7.3.1 Deaths

There were no deaths.

7.3.2 Nonfatal Serious Adverse Events

One patient had a serious adverse event. This was a 45-year-old, Hispanic female subject who was assigned to Sequence C (1-2-3-1-2) in the study. She received her final dose of study drug (a single mesalamine delayed release capsule, 400 mg) in the fasted state on (b) (6) and went on to complete the study. On (b) (6) she experienced severe epigastric pain (subsequently diagnosed as pancreatitis) that was considered by the Investigator to be treatment-related. The pain recurred on (b) (6) and (b) (6)

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

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

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

7.3.3 Dropouts and/or Discontinuations

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

- Subject (b) (6)
  Mild lower back pain considered by the Investigator not related to study drug.
- Subject (b) (6)
  Mild sinus congestion considered by the Investigator not related to study drug.
- Subject (b) (6)
  Moderate headache considered by the Investigator to be related to study drug..
- Subject (b) (6)
  Mild nausea considered by the Investigator to be related to study drug. The

7.3.4 Significant Adverse Events

No significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission-specific safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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

7.4.2 Laboratory Findings

No clinically significant abnormal l laboratory values were identified.

7.4.3 Vital Signs

No clinically significant vital sign abnormalities were noted.

7.4.4 Electrocardiograms (ECGs)

No clinically significant ECG abnormalities were noted.

7.4.5 Special Safety Studies/Clinical Trials

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

7.4.6 Immunogenicity

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

7.5 Other Safety Explorations

No other safety explorations were performed.

7.5.1 Dose Dependency for Adverse Events

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

7.5.2 Time Dependency for Adverse Events

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

7.5.3 Drug-Demographic Interactions

No drug-demographic interactions were explored.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were explored.

7.5.5 Drug-Drug Interactions

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

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

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

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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

7.6.2 Human Reproduction and Pregnancy Data

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

Risk Summary

(b) (4)

Data

Animal Data

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

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

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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

7.7 Additional Submissions / Safety Issues

No additional safety submissions were received during the review cycle.

8 Postmarketing Experience

Table 7: Distribution Data for Delzicol delayed-release capsules

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

Electronically copied and reproduced from Annual Report Feb 2014-Jan 2015 Distribution Data Table 1

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

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

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

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

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

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

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

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

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

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

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

9.3 Advisory Committee Meeting

No advisory committee meeting was held regarding this application.

9.4

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

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

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject (b) (6) had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.
Source: Listing 16.2.7.1
WC3079/PR-07513/programs/production/safety/aesocpt.sas SAS 9.2 09/25/2014 8:11

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

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject (b) (6) had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.

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

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject (b) (6) had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.

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

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject (b) (6) had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.

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

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject (b) (6) had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.
Source: Listing 16.2.7.1

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

Note: This table presents the number (%) of subjects with at least one event in the respective category.
Subject (b) (6) had an ARTHROPOD BITE without an associated treatment. This AE is captured here in the Total column.
Source: Listing 16.2.7.1

Electronically copied and reproduced from PR-07513 CSR Table 14.3.1.2 pgs 210-15

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/s/

MARJORIE F DANNIS
08/05/2015

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

CHEMISTRY REVIEW(S)

Chemistry Review: #1 Amendment	**1. Division:** HFD-DGEIP	**2. NDA Number** 204-412

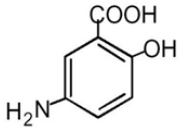
3. Name and Address of Applicant: Warner Chilcott (US) LLC 100 Enterprise Drive Rockaway, NJ 07866	**4. Supplement(s): Pediatric Efficacy, PA Number: 006 Date(s): November 10, 2014 Stamped: November 12, 2014 Due: August 5, 2015**
4. Name of Drug: Delzicol	**5. Nonproprietary name:** (mesalamine) Delayed Release Capsules WC3079

7. Supplement Provides for : A Prior approval Efficacy supplement to fulfill the Required Pediatric Equity Act by the replacing the current Delzicol capsules, 400 mg, with Delzicol (mesalamine) Delayed-Release Capsules (4 x 100 mg tablets).	**8. Amendment(s):** None

9. Pharmacological Category: Treatment of mildly to moderately active Ulcerative Colitis (UC).	**10. How Dispensed:** R_x	**11. Related Documents:** None

12. Dosage Form: Capsules .	**13. Potency:** 400 mg

14. Chemical Name and Structure: 5-amino-2-hydroxybenzoic acid.



Molecular weight: 153.1
Molecular Formula: $C_7H_7NO_3$

16. Comments: Review #1 of this supplement recommended approval. This amendment to review #1 is for the inclusion of the applicant's request for a categorical exclusion from the requirement to prepare an environmental assessment report for the active drug substance, mesalamine. The applicant's rationale is as follows:

14. ENVIRONMENTAL ASSESSMENT

WC3079 capsule (4 x 100 mg), a pediatric suitable formulation, will not increase the use of the active moiety, mesalamine, because WC3079 capsules will directly replace an approved product Delzicol capsule, once WC3079 capsules are approved by the Division.

Based on the criteria outlined in 21 CFR §25.31(a) and *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (July 1998)*, Warner Chilcott is filing a claim of categorical exclusion from the requirement to prepare an environment assessment for the active moiety, mesalamine.

Evaluation: The rationale provided is adequate and acceptable. The Categorical Exclusion request is granted.

17. Conclusion: The Categorical Exclusion request is granted. From the CMC point of view, this supplement is recommended for approval.

17. Name: Libaniel Rodriguez, Ph.D. Review Chemist/OPS/OLDP/DPMA1/BII
Signature: **Date:**

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/s/

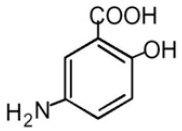
LIBANIEL RODRIGUEZ
09/08/2015
Amendment to include adequate EA statement

Chemistry Review: #1	**1. Division:** HFD-	**2. NDA Number** 204-412

3. Name and Address of Applicant: Warner Chilcott (US) LLC 100 Enterprise Drive Rockaway, NJ 07866	**4. Supplement(s): Pediatric Efficacy, PA** **Number:** 061 **Date(s): November 10, 2014** **Stamped: November 12, 2014** **Due: August 5, 2015**
4. Name of Drug: Delzicol	**5. Nonproprietary name:** (mesalamine) Delayed Release Capsules WC3079

7. Supplement Provides for : A Prior approval Efficacy supplement to fulfill the Required Pediatric Equity Act by the replacing the current Delzicol capsules, 400 mg, with Delzicol (mesalamine) Delayed-Release Capsules (4 x 100 mg tablets).		**8. Amendment(s):** None
9. Pharmacological Category: Treatment of mildly to moderately active Ulcerative Colitis (UC).	**10. How Dispensed:** R_x	**11. Related Documents:** None
12. Dosage Form: Capsules .	**13. Potency:** 400 mg	

14. Chemical Name and Structure: 5-amino-2-hydroxybenzoic acid.



Molecular weight: 153.1
Molecular Formula: $C_7H_7NO_3$

16. Comments: Asacol® (mesalamine) delayed-release tablets, 400 mg (NDA 19-651), was approved in January 1992 for the treatment of mildly to moderately active ulcerative colitis (UC).

Because of the presence of dibutyl phthalate (DBP) as an excipient in the asacol tablet, the applicant developed a DBP free formulation in a new dosage form, mesalamine delayed-release capsules, 400 mg (Delzicol capsules, WC3045)), in which the plasticizer DBP in the tablet enteric coat was replaced with dibutyl sebacate (DBS) and the tablet was then encapsulated. The NDA for Delzicol capsules (NDA 204-412) was approved in February 2013. The approval letter for Delzicol capsules waived the pediatric requirement for children ages 0 to less than 5 years, and deferred submission of the pediatric studies for children 5 to 17 years.

To fulfill the Pediatric requirement above, the applicant developed a DBP free formulation, mesalamine delayed-release capsules, (WC3079 capsules) intended for use in patients 5 years and older. Each WC3079 capsule contains four 100 mg mesalamine tablets.

There are no changes to the drug substance, excipients, capsule, manufacturing procedures, analytical testing or container closure, in the manufacturing of the proposed WC3079 capsules from the components and procedures currently approved for the manufacture of Delzicol capsules .

The applicant intends to replace the currently approved Delzicol capsules, 400 mg, for the WC3079 capsules upon approval of this efficacy supplement.

Most of the CMC information and data provided in support of the proposed WC3079 capsules is the same as the information that was approved in NDA 402-412 for Delzicol capsules. Minor changes to accommodate the manufacturing of the proposed WC3079 capsules were made. In addition stability data for the proposed capsules and revised labeling for the proposed capsules were submitted in this application.

Details of the minor changes in manufacturing and discussion of the stability data and labeling can be seen in the Chemistry Review Notes section of this review.

The Biopharmaceutical reviewer, Dr. Peng Duan, reviewed all the dissolution data provided in support of this application, as well as all other biopharmaceutical aspects of this application, and recommended the application for approval on **July 6, 2015**. See copy of the biopharm review (entered in Panorama on August 11, 2015) conclusions attached at the end of this review.

The overall recommendation from the Office of Process and Facilities (OPF) for the manufacturing and testing facilities is **Approval,** May 12,2015. See copy of OPF report in Panorama, attached to the end of this review.

17. Conclusion: All the CMC information and data provided in support of this application is **acceptable**. The Office of Process and Facilities (OPF) recommended the manufacturing site(s) for **approval** . The BioPharm review recommended the application for **approval.** For these reasons from the point of view of CMC this application is recommended for **Approval.**

17. Name: Libaniel Rodriguez, Ph.D. Review Chemist/OPS/OLDP/DPMA1/BII
Signature: **Date:**

18. Concurrence: **Signature:** **Date:**
Thomas Oliver, Ph.D., DD/ONDQA/DNDQAII

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Conclusion: All the CMC information and data provided in support of this application is **acceptable**. The Office of Process and Facilities (OPF) recommended the manufacturing site(s) for **approval** . The BioPharm review recommended the application for **approval.** For these reasons from the point of view of CMC this application is recommended for **Approval.**

NDA-204412-SUPPL-6 - Manufacturing Facility Inspection

(b) (4)

[redacted]

Recommendations:

From the Biopharmaceutics perspective, the NDA efficacy supplement 204412 S-006 for Delzicol (mesalamine) Delayed-Release Capsules, 400 mg, is recommended for approval.

Signature

Peng Duan -S

Vincent (Peng) Duan, Ph.D.
Biopharmaceutics reviewer
Office of New Drug Products

Signature

Kelly M. Kitchens -S

Digitally signed by Kelly M. Kitchens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000336574, cn=Kelly M. Kitchens -S
Date: 2015.08.05 19:58:19 -04'00'

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Quality Assessment Lead
Office of New Drug Products

Cc. TGhosh; PSeo

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/s/

LIBANIEL RODRIGUEZ
08/27/2015

THOMAS F OLIVER
08/27/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	204412
Supporting document/s:	S-006
Sponsor's letter date:	November 11, 2014
CDER stamp date:	November 12, 2014
Product:	Delzicol (Mesalamine) Delayed-Release Capsules, (400 mg)
Indication:	Treatment of mild to moderate ulcerative colitis in pediatric patients aged 5 years and older
Sponsor:	Warner Chilcott
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Sushanta Chakder, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Kelly Richards, RN

Background: Delzicol (asacol) delayed release capsules are currently approved for the treatment of moderately active ulcerative colitis in adult patients. Warner Chilcott submitted a pediatric efficacy supplement seeking an approval for use of delzicol delayed release capsules for the treatment of mild to moderate ulcerative colitis (UC) in pediatric patients aged 5 years and older. The applicant has developed a new mesalamine delayed-release capsule formulation for use in patients 5 years and older. Each capsule contains four 100 mg mesalamine tablets, and the tablets can be administered individually. No nonclinical studies were submitted under the current pediatric efficacy supplement.

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, the pediatric efficacy supplement is recommended for approval.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

In the draft labeling, the applicant did not propose any changes in the nonclinical sections (Sections 8.1, 13.1 and 13.2) of the existing label for Delzicol Capsules. The recommended version of Sections 8 and 13 is provided below.

8.1 Pregnancy

Risk Summary

(b) (4)

Data

Animal Data

Reproduction studies with mesalamine were performed during organogenesis in rats and rabbits at oral doses up to 480 mg/kg/day. There was no evidence of impaired fertility or harm to the fetus. These 480 mg/kg/day dose of mesalamine is about 1.9 times (rat) and 3.9 times (rabbit) (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mesalamine was not carcinogenic at dietary doses of up to 480 mg/kg/day in rats and 2000 mg/kg/day in mice, which are about (b) (4).9 and (b) (4)1 times the maximum recommended (b) (4) dose of DELZICOL of (b) (4)/ per day or (b) (4) mg/kg/day, based on 60 kg body weight, respectively, based on body surface area.

Mutagenesis

Mesalamine was negative in the Ames assay for mutagenesis, negative for induction of sister chromatid exchanges (SCE) and chromosomal aberrations in Chinese hamster ovary cells in vitro, and negative for induction of micronuclei (MN) in mouse bone marrow polychromatic erythrocytes.

Impairment of Fertility

Mesalamine, at oral doses up to 480 mg/kg/day (about 1.9 times the recommended human treatment dose on a body surface area basis), was found to have no effect on fertility or reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

In animal studies (rats, mice, dogs), the kidney was the principal organ for toxicity. (In the following, comparisons of animal dosing to recommended human dosing are based on body surface area and a 2.4 g/daygrams per day dose for a 60 kg person.)

Mesalamine causes renal papillary necrosis in rats at single doses of approximately 750 mg/kg to 1000 mg/kg (approximately 3 to 4 times the recommended human dose based on body surface area). Doses of 170 and 360 mg/kg/day (about 0.7 and 1.5 times the recommended human dose based on body surface area) given to rats for six months produced papillary necrosis, papillary edema, tubular degeneration, tubular mineralization, and urothelial hyperplasia.

In mice, oral doses of 4000 mg/kg/day mesalamine (approximately 8 times the recommended human dose based on body surface area) for three months produced tubular nephrosis, multifocal/diffuse tubulo-interstitial inflammation, and multifocal/diffuse papillary necrosis.

In dogs, single doses of 6000 mg (approximately 8 times the recommended human dose based on body surface area) of delayed-release mesalamine tablets resulted in renal papillary necrosis but were not fatal. Renal changes have occurred in dogs given chronic administration of mesalamine at doses of 80 mg/kg/day (1.1 times the recommended human dose based on body surface area).

Summary and Evaluation

Asacol (mesalamine) is a locally acting aminosalicylate, indicated for the treatment of mildly to moderately active ulcerative colitis (UC). Delzicol (asacol) delayed release capsules are currently approved for the treatment of moderately active ulcerative colitis in adult patients. To fulfil the PREA requirement for Delzicol capsules, the applicant submitted a pediatric efficacy supplement seeking an approval for use of delzicol delayed release capsules for the treatment of mild to moderate ulcerative colitis (UC) in pediatric patients aged 5 years and older. The applicant has developed a new mesalamine delayed-release capsule formulation for use in patients 5 years and older. Each capsule contains four 100 mg mesalamine tablets. Based on extensive clinical experience with mesalamine products in pediatric subjects and no serious safety issues, no juvenile animal toxicity studies were required in support of the safety of the drug in pediatric patients. The applicant submitted the updated labeling for Asacol tablets. No changes for the nonclinical Sections (Sections 8.1, 13.1 and 13.2) of the existing label were proposed. Few changes in the nonclinical sections of the proposed label is recommended.

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/s/

SUSHANTA K CHAKDER
08/05/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

STATISTICAL REVIEW(S)

US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

New Drug Application

Biometrics Division: VI

NDA NO.:	204412
DATE RECEIVED BY OB:	03/31/2015
DRUG NAME:	Delzicol(mesalamine) delayed release capsules
INDICATION:	Treatment Of Mildly To Moderately Active Ulcerative Colitis; Maintenance Of Remission Of Ulcerative Colitis.
SPONSOR:	Warner Chilcott
REVIEW FINISHED:	07/31/2015
NAME OF STATISTICAL REVIEWER:	Zhuang Miao, Ph.D.
DCP REVIEWERS:	Sue Chih Lee, Ph.D. Sandhya Apparaju, Ph.D.

Secondary Reviewer:

Meiyu Shen, Ph.D., Team Leader, Mathematical Statistician, CDER/OTS/OB/DB VI

Concur:

Yi Tsong, Ph.D., Division Director, DBVI, CDER/OTS/OB/DB VI

Distribution:

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CDER/OND/ODEIII/DGIEP Anil Rajpal
CDER/OND/ODEIII/DGIEP Marjorie Dannis
CDER/OND/ODEIII/DGIEP Kelly Richards
CDER/OND/ODEIII/DGIEP Kevin Bugin

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1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

1.1 Purpose of this review

On March 31, 2015, Office of Clinical Pharmacology (OCP) requests CMC statistics team in the Office of Biostatistics (OB) to evaluate Warner Chilcott Company's 5-period crossover bioequivalence trial for the relative bioavailability of a new Delzicol (mesalamine) delayed release formulation WC3079 vs. the approved Delzicol 400 mg formulation. The sponsor proposed to remove the food-effect period and then collapse the 5-period design into a 4-period design. Particularly, OCP requests OB to conduct analyses without removing the food-effect period for the bioequivalence portion of the study (primary objective) in order to determine if this approach by the sponsor has affected the outcomes of the BE analysis.

1.2 Sponsor's crossover design

In order to evaluate the bioavailability of Delzicol delayed-release capsules, 400 mg, vs Asacol (mesalamine) delayed-release tablets, 400mg, a 4-sequence, 5-period, 3-treatment crossover study was conducted. The specific design is shown in **Table 1**,

Table 1: Study Design

	Period p_j				
Sequence g_i	1	2	3	4	5
1	Trt_1	Trt_3	Trt_2	Trt_1	Trt_2
2	Trt_2	Trt_1	Trt_2	Trt_3	Trt_1
3	Trt_1	Trt_2	Trt_3	Trt_1	Trt_2
4	Trt_2	Trt_1	Trt_3	Trt_2	Trt_1

Trt_1 = Asacol, fasted; Trt_2 = Delzicol, fasted; Trt_3 = Delzicol, fed

Note that we denote the population mean of Delzicol as μ_T , fasted and denote the population mean of Asacol as μ_R in the following sections.

1.3 FDA's information requests and the sponsor's responses to FDA IRs

During the review cycle, FDA (CMC statistics team) sent multiple information requests to the sponsor in order to facility the review.

On April 22, 2015, FDA sent out information request below,

"With regard to NDA 204412/S-006, it appears that during your statistical analyses to test for bioequivalence under fasting conditions, you've re-numbered periods by removing the fed-treatment period. A similar approach was used in the analysis to evaluate the food-effect. This assumes absence of a period effect. In this regard, we recommend that you repeat the statistical analyses for each of the two objectives without eliminating periods. Please submit your new

analyses and conclusions within two weeks after receipt of this information request. If this date cannot be met, please contact us as soon as possible."

On April 30, 2015, the sponsor submitted their request for clarification,

"For the 2 objectives, bioequivalence (BE) of Delzicol vs Asacol, and food effect of fed vs fasted Delzicol, the relevant PK parameters are analyzed in 2 different ways:

1. Reference-scaled BE, the primary analysis discussed in the body of the CSR, and the correct model given the high variability (the within-reference SD > 0.294 for all parameters, corresponding to CV > 30%)
2. Unscaled average BE, which is not correct given the high variability, but is the standard model under low variability: these additional analyses are provided only in after-text tables and not discussed in the CSR

The CSR for study PR-07513 only discusses the reference-scaled approach and all conclusions are based on these models. The study was powered under these assumptions as well, so the protocol developers were aware at that time that these drugs are highly variable, and as such, followed the guidance for highly variable drug products, described here:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm209294.pdf

By the nature of the reference-scaled approach, each patient's individual log PK scores for the 5 periods are reduced to a single term for the respective BE and FE models:

1. Bioequivalence of Delzicol vs Asacol:

T_{ijk} = kth observation (k = 1 or 2) on T for subject j within sequence i

R_{ijk} = kth observation (k = 1 or 2) on R for subject j within sequence i

$$I_{ij} = \frac{T_{ij1} + T_{ij2}}{2} - \frac{R_{ij1} + R_{ij2}}{2}$$

2. Food effect of fed vs fasted Delzicol:

T_{ij} = the observation on T for subject j within sequence i

R_{ijk} = kth observation (k = 1 or 2) on R for subject j within sequence i

$$I_{ij} = T_{ij} - \frac{R_{ij1} + R_{ij2}}{2}$$

The ANOVA models used in this approach cannot contain either treatment or period (or carryover), since each patient's data is reduced to a single term for each respective model. The ANOVA models only controls for sequence per the guidance.

Request for Clarification of the statistical information request:

We would like to request clarification of which model part 1 of the information request refers to. If the statistical reviewer's question pertains to the reference-scaled BE model, treatment or period cannot be added to the reference scaled-model and therefore we would like to verify if the information request in part 2 of the information request (pdf attachment) is relevant since the estimators outlined in the pdf attachment, treatment and period, are not applicable to the reference scaled-model.

Please confirm the statistical reviewer's main objective of the information request. Is the goal of the fulfillment of the statistical information request to support the study data analysis conclusion that there was a lack of carryover effect?"

On May 11, 2015, we sent out our clarification below:

"Since Delzicol is a highly variable drug, use of the reference-scaled average BE approach is appropriate. However, the methods in the reference-scaled average BE guidance are only applicable to the particular designs (with balanced periods) as specified in that guidance, and not to any other designs. For those particular designs, the estimator for the treatment difference between the test and the reference is unbiased even if no carryover effect is assumed. Because your design is different from those specified in the reference-scaled average BE guidance, your estimator for the treatment difference between the test and the reference is biased when you assume no carryover effect. You must therefore find the unbiased estimator for the treatment difference between the test and the reference without any assumption of the period effect. Please refer to the previous communication for details on the appropriate methods."

On May 28, 2015, the sponsor submitted their response to information request. They provided their methods in terms of statistical formula.

For the bioavailability analysis, the sponsor removed Trt_3, as shown in Table 2,

Table 2: Study Design excluding $\mathbf{Trt_3}$

	Period p_j				
Sequence g_i	1	2	3	4	5
1	Trt_1	~~Trt_3~~	Trt_2	Trt_1	Trt_2
2	Trt_2	Trt_1	Trt_2	~~Trt_3~~	Trt_1
3	Trt_1	Trt_2	~~Trt_3~~	Trt_1	Trt_2
4	Trt_2	Trt_1	~~Trt_3~~	Trt_2	Trt_1

Trt_1 = Asacol, fasted; Trt_2 = Delzicol, fasted; ~~Trt_3 = Delzicol, fed~~

The statistical model for response y_{ijk}, sample means, and expectations are given below:

$$y_{ijk} = \tau + \mu_{(j,i)} + g_i + pj + c_{(j-1,i)} + s_{ki} + \epsilon_{ijk}$$

$$\bar{y}_{ij.} = \frac{\sum_{k=1}^{n_i} y_{ijk}}{n_i}, \text{ sample mean for sequence } i \text{ in period } j$$

$$E\left[y_{ijk}\right] = \tau + \mu_{(j,i)} + g_i + pj + c_{(j-1,i)}$$

where

y_{ijk} = response of subject k in sequence i and period j
$i \in \{1,2,3,4\}, j \in \{1,2,3,4,5\}, k \in \{1,2,\ldots,n_i\}$

τ = overall mean effect

$\mu_{(j,i)}$ = direct effect of treatment in sequence i and period j

g_i = fixed effect of sequence i

p_j = fixed effect of period j

$c_{(j-1,i)}$ = fixed effect of first-order carryover of treatment in sequence i from period $j-1$ for $j \in \{2,3,4,5\}$; we assume no higher-order carryover effects

s_{ki} = between-subject random effect, subject within sequence i

ϵ_{ijk} = within-subject random error for response y_{ijk}

n_i = number of subjects randomized to sequence i

The sample means and their expectations for the sequence-by-period cells are given in Table 1

Table 3, sample means and expected values by sequence and period

	Period p_j				
Sequence g_i	1	2	3	4	5
1	$\bar{y}_{11.}$ $\tau+\mu_1+g_1+p_1$	$\bar{y}_{12.}$ $\tau+\mu_3+g_1+p_2+c_1$	$\bar{y}_{13.}$ $\tau+\mu_2+g_1+p_3+c_3$	$\bar{y}_{14.}$ $\tau+\mu_1+g_1+p_4+c_2$	$\bar{y}_{15.}$ $\tau+\mu_2+g_1+p_5+c_1$
2	$\bar{y}_{21.}$ $\tau+\mu_2+g_2+p_1$	$\bar{y}_{22.}$ $\tau+\mu_1+g_2+p_2+c_2$	$\bar{y}_{23.}$ $\tau+\mu_2+g_2+p_3+c_1$	$\bar{y}_{24.}$ $\tau+\mu_3+g_2+p_4+c_2$	$\bar{y}_{25.}$ $\tau+\mu_1+g_2+p_5+c_3$
3	$\bar{y}_{31.}$ $\tau+\mu_1+g_3+p_1$	$\bar{y}_{32.}$ $\tau+\mu_2+g_3+p_2+c_1$	$\bar{y}_{33.}$ $\tau+\mu_3+g_3+p_3+c_2$	$\bar{y}_{34.}$ $\tau+\mu_1+g_3+p_4+c_3$	$\bar{y}_{35.}$ $\tau+\mu_2+g_3+p_5+c_1$
4	$\bar{y}_{41.}$ $\tau+\mu_2+g_4+p_1$	$\bar{y}_{42.}$ $\tau+\mu_1+g_4+p_2+c_2$	$\bar{y}_{43.}$ $\tau+\mu_3+g_4+p_3+c_1$	$\bar{y}_{44.}$ $\tau+\mu_2+g_4+p_4+c_3$	$\bar{y}_{45.}$ $\tau+\mu_1+g_4+p_5+c_2$

Based on this study design, the naïve estimator for $\mu_2 - \mu_1$, $\widehat{D}_1$ and expected value, $\mathrm{E}[\widehat{D}_1]$ are respectively given below,

$$\hat{D}_1 = \frac{1}{4}\begin{bmatrix} +\left(\frac{\bar{y}_{13.}+\bar{y}_{15.}}{2}\right) & - & \left(\frac{\bar{y}_{11.}+\bar{y}_{14.}}{2}\right) \\ +\left(\frac{\bar{y}_{21.}+\bar{y}_{23.}}{2}\right) & - & \left(\frac{\bar{y}_{22.}+\bar{y}_{25.}}{2}\right) \\ +\left(\frac{\bar{y}_{32.}+\bar{y}_{35.}}{2}\right) & - & \left(\frac{\bar{y}_{31.}+\bar{y}_{34.}}{2}\right) \\ +\left(\frac{\bar{y}_{41.}+\bar{y}_{44.}}{2}\right) & - & \left(\frac{\bar{y}_{42.}+\bar{y}_{45.}}{2}\right) \end{bmatrix} = \frac{1}{4}\left(\frac{1}{2}\right)\begin{bmatrix} -\bar{y}_{11.} & & +\bar{y}_{13.} & -\bar{y}_{14.} & +\bar{y}_{15.} \\ +\bar{y}_{21.} & -\bar{y}_{22.} & +\bar{y}_{23.} & & -\bar{y}_{25.} \\ -\bar{y}_{31.} & +\bar{y}_{32.} & & -\bar{y}_{34.} & +\bar{y}_{35.} \\ +\bar{y}_{41.} & -\bar{y}_{42.} & & +\bar{y}_{44.} & -\bar{y}_{45.} \end{bmatrix}$$

$$E\left[\hat{D}_1\right] = (\mu_2 - \mu_1) + \frac{1}{8}(-p_2 + 2p_3 - p_4) + \frac{1}{2}(c_1 - c_2)$$

.

The sponsor also proposed another design excluding more cells in the original design in order to use the guidance method on partial reference-replicated 3-way design. The naïve estimator for$\mu_2 - \mu_1$, $\widehat{D}_{1B}$ and expected value, E[$\widehat{D}_{1B}$] are giving below,

$$\hat{D}_{1B} = \frac{1}{4}\begin{bmatrix} +\left(\bar{y}_{15.} & - & \frac{\bar{y}_{11.}+\bar{y}_{14.}}{2}\right) \\ +\left(\bar{y}_{21.} & - & \frac{\bar{y}_{22.}+\bar{y}_{25.}}{2}\right) \\ +\left(\bar{y}_{32.} & - & \frac{\bar{y}_{31.}+\bar{y}_{34.}}{2}\right) \\ +\left(\bar{y}_{44.} & - & \frac{\bar{y}_{42.}+\bar{y}_{45.}}{2}\right) \end{bmatrix} = \frac{1}{4}\left(\frac{1}{2}\right)\begin{bmatrix} -1\bar{y}_{11.} & & -1\bar{y}_{14.} & +2\bar{y}_{15.} \\ +2\bar{y}_{21.} & -1\bar{y}_{22.} & & -1\bar{y}_{25.} \\ -1\bar{y}_{31.} & +2\bar{y}_{32.} & -1\bar{y}_{34.} & \\ & -1\bar{y}_{42.} & +2\bar{y}_{44.} & -1\bar{y}_{45.} \end{bmatrix}$$

$$E\left[\hat{D}_{1B}\right] = (\mu_2 - \mu_1) + \frac{1}{2}(c_1 - c_2)$$

On June 8, 2015, FDA sent out the information request as below,

"For the BE evaluation, your unbiased estimate is incorrect because it appears that you intentionally take away some observations for the test product (See Page 5 in your response). It is possible to find an unbiased estimator with all observations in Periods 1, 2, 4, and 5. It is acceptable to remove the observations in Period 3. Find another unbiased estimator for the treatment difference and submit the mathematical and statistical formulas and SAS codes for calculating the confidence interval for $(\mu_T - \mu_R)^2 - \theta\sigma_{WR}^2$ *."*

On June 11, 2015, FDA sent out the information request regarding the unbalanced number of number of nonzero concentrations (⩽3) for the reference product than those for the test product,

"1)

*Table **4** shows that there are more cases with the small number of nonzero concentrations (⩽3) for the reference product than those for the test product.*

Can you scientifically justify the observed differences?

How do you justify your analysis to support the equivalence between the reference product and the test product when 23% of subjects have at least one case with the small number of nonzero concentration (⩽3)?

2)

*Table **5** shows that the naïve biased estimate for* μ_T / μ_R *in the subgroup with >3 nonzero concentrations is 0.72, which is much smaller than 0.96 if all observations are included. In other words, the geometric mean of the responding subjects with >3 nonzero concentrations in the test group is too small compared to that of the responding subjects in the reference group.*

How do you assure the efficacy of the test product for the responding subgroup with >3 nonzero concentrations since the equivalence trial does not address either the efficacy or the safety issue?

Table 4: Distribution of the number of nonzero concentrations

Number of nonzero concentrations	*Number of subjects*	
	Reference	*Test*
0	*15*	*2*
≤1	*17*	*8*
≤2	*20*	*9*
≤3	*26*	*12*

Table 5: Sample mean and sample standard deviation of log(AUC) of the subgroup with >3 nonzero concentrations for each treatment

Treatment	*Number of subjects*	*Sample mean of log(AUC)*	*Sample standard deviation of log(AUC)*
R1 (first trt1 in each sequence)	*112*	*6.662*	*0.730*
R2 (second trt1 in each sequence)	*112*	*6.716*	*0.677*
T1(first trt2 in each sequence)	*112*	*6.417*	*0.703*
T2 (second trt2 in each sequence)	*112*	*6.308*	*0.854*

”

The sponsor submitted their response on June 24, 2015.

“Sponsor Response to questions 1:

The reference product (Asacol tablets, 400mg) and test product (WC3079, 4x100 mg) utilize a delayed-release pH-dependent delivery system to release the drug in the lower gastrointestinal tract (mostly in the colon). Given the typically lower volumes of fluid present in the colon and variable pH profiles & gastric transit times of the GI tract between and within patients, the release of the drug is expected to be somewhat variable and possibly incomplete at times. The use of 4 tablets (100 mg each) of the test product as compared to a single tablet of the reference product, is expected to provide a more robust release profile. This is based on the understanding

that the drug release from 4 units should buffer against any inherent variability and result in a more uniform profile as compared to release from a single unit.

Sponsor Response to questions 2:

The BE analysis was a prospectively planned statistical analysis, in compliance with the "Statistical Approaches to Establishing Bioequivalence" guidance from the FDA. Although there are more cases with a small number of nonzero concentrations ($\leqslant 3$) for the reference product compared to the test product, removing these data from either group cannot be justified since it is probably a reflection of observations in a real-world setting and since, as per the above-referenced guidance, deletion of outlier data, e.g. subjects with 0-3 measurable concentrations, is generally discouraged in pivotal BE studies. Deleting the observed data from subjects with only 0-3 measurable concentrations results in a biased overestimation of the mean for the reference product as compared to the test product.

Sponsor Response to questions 3:

As noted in the response above, removing the data from subjects with <=3 concentrations cannot be justified; this results in a biased overestimation of the reference product mean which does not reflect a real-world setting. Based on the prespecified analysis and in accordance with recommendations in the FDA guidance "Statistical Approaches to Establishing Bioequivalence", there is no significant difference in overall exposure between the test and reference products."

On June 24, 2015, FDA sent out the information request as follows,

"Since your study is not properly designed to obtain unbiased estimate of treatment difference, you may only be able to obtain unbiased estimate by using a fraction of the data collected in the study. However, there may be various ways to achieve this objective. Please provide all the possible unbiased estimators for the treatment difference without removing any of the treatments from Periods 1, 2, 4, 5. Justify the unbiased estimators in terms of mathematical and statistical formulas and conduct hypothesis testing using all unbiased estimators. Submit the mathematical and statistical formulas, SAS codes for calculating the confidence interval for $(\mu_T - \mu_R)^2 - \theta\sigma_{WR}^2$ *and the SAS output to support bioequivalence. Submit this information within 3 weeks. "*

On July 1, 2015, we had a TCON with the sponsor. After the teleconference, FDA sent out another information request, "Since you are proposing modeling approach for estimation, please provide both analyses for only fasted data and the combined data of the fasted and fed studies" on July 7, 2015

On July 15, 2105, the sponsor submitted their response with another four modified design and estimators. The sponsor removed the third period, and the naïve estimator for$\mu_2 - \mu_1$, $\widehat{D}_{1C}$ and expected value, E[$\widehat{D}_{1C}$] are giving below,

$$\hat{D}_{1C} = \frac{1}{5}\begin{bmatrix} +\left(\bar{y}_{15.} - \frac{\bar{y}_{11.}+\bar{y}_{14.}}{2}\right) \\ +\left(\bar{y}_{21.} - \frac{\bar{y}_{22.}+\bar{y}_{25.}}{2}\right) \\ +\left(\frac{2\bar{y}_{32.}+\bar{y}_{35.}}{2} - \frac{2\bar{y}_{31.}+\bar{y}_{34.}}{2}\right) \\ +\left(\frac{\bar{y}_{41.}+2\bar{y}_{44.}}{2} - \frac{\bar{y}_{42.}+2\bar{y}_{45.}}{2}\right) \end{bmatrix} = \frac{1}{5}\left(\frac{1}{2}\right)\begin{bmatrix} -1\bar{y}_{11.} & & -1\bar{y}_{14.} & +2\bar{y}_{15.} \\ +2\bar{y}_{21.} & -1\bar{y}_{22.} & & -1\bar{y}_{25.} \\ -2\bar{y}_{31.} & +2\bar{y}_{32.} & -1\bar{y}_{34.} & +1\bar{y}_{35.} \\ +1\bar{y}_{41.} & -1\bar{y}_{42.} & +2\bar{y}_{44.} & -2\bar{y}_{45.} \end{bmatrix}$$

$$E\left[\hat{D}_{1C}\right] = (\mu_2 - \mu_1) + \frac{1}{2}(c_1 - c_2)$$

For the fourth estimator, the sponsor kept all the cells in the design. The naïve estimator for$\mu_2 - \mu_1$, $\widehat{D}_{1D}$ and expected value, E[$\widehat{D}_{1D}$] are giving below,

$$\hat{D}_{1D} = \frac{1}{5}\begin{bmatrix} +\left(\frac{\bar{y}_{13.}+\bar{y}_{15.}}{2} - \frac{3\bar{y}_{11.}+3\bar{y}_{14.}}{4} + \frac{\bar{y}_{12.}}{2}\right) \\ +\left(\frac{\bar{y}_{21.}+\bar{y}_{23.}}{2} - \frac{3\bar{y}_{22.}+3\bar{y}_{25.}}{4} + \frac{\bar{y}_{24.}}{2}\right) \\ +\left(\frac{3\bar{y}_{32.}+3\bar{y}_{35.}}{4} - \frac{\bar{y}_{31.}+\bar{y}_{34.}}{2} - \frac{\bar{y}_{33.}}{2}\right) \\ +\left(\frac{3\bar{y}_{41.}+3\bar{y}_{44.}}{4} - \frac{\bar{y}_{42.}+\bar{y}_{45.}}{2} - \frac{\bar{y}_{43.}}{2}\right) \end{bmatrix} = \frac{1}{5}\left(\frac{1}{4}\right)\begin{bmatrix} -3\bar{y}_{11.} & +2\bar{y}_{12.} & +2\bar{y}_{13.} & -3\bar{y}_{14.} & +2\bar{y}_{15.} \\ +2\bar{y}_{21.} & -3\bar{y}_{22.} & +2\bar{y}_{23.} & +2\bar{y}_{24.} & -3\bar{y}_{25.} \\ -2\bar{y}_{31.} & +3\bar{y}_{32.} & -2\bar{y}_{33.} & -2\bar{y}_{34.} & +3\bar{y}_{35.} \\ +3\bar{y}_{41.} & -2\bar{y}_{42.} & -2\bar{y}_{43.} & +3\bar{y}_{44.} & -2\bar{y}_{45.} \end{bmatrix}$$

$$E\left[\hat{D}_{1D}\right] = (\mu_2 - \mu_1) + \frac{1}{2}(c_1 - c_2)$$

In addition to the estimators above, the sponsor provides two estimators based on the standard average bioequivalence MMRM model, $\widehat{D}_{1E}$, based on all data and $\widehat{D}_{1F}$, excluding fed data.

Table 6 shows the ranges of the geometric mean ratio and linearized upper confidence bound estimates over the presented estimators for each parameter obtained by the sponsor.

Table 6: Ranges of Geometric Mean Ratio and Linearized Upper Confidence Bound Estimates over Estimators by Parameter

	Ratio		LUCB	
Parameter	Min	Max	Min	Max
C_{max}	111.88	119.10	-1.138	-1.077
AUC_{8-48}	93.24	97.41	-1.583	-1.531
AUC_{0-tldc}	102.09	106.22	-1.573	-1.525
AUC_{0-inf}	84.97	94.78	-0.256	-0.189

Ratio = geometric mean ratio Trt2/Trt1; LUCB = linearized upper confidence bound.

1.4 Statistical issues

There are multiple statistical issues from the sponsor's crossover design and the response to the FDA IRs:

1. Imbalance of the number of zero profiles in WC3079 (test) and Asacol (reference)

As we pointed out in the information request dated on June 11, 2015, there are more cases with the small number of nonzero concentrations ($\leqslant 3$) for the reference product than those for the test product (see Table 4).

2. The naïve biased estimate for μ_T / μ_R in the subgroup with >3 nonzero concentrations smaller than 0.8

   From Table 5, the naïve biased estimate for μ_T / μ_R in the subgroup with >3 nonzero concentrations is 0.72, which is smaller than 0.8 (point estimate criteria in Scaled-average BE) and is much smaller than 0.96 if all observations are included. Hence, the geometric mean of the responding subjects with >3 nonzero concentrations in the test group is too small compared to that of the responding subjects in the reference group.

3. Design flaw and biased estimator $\widehat{\mathrm{D}}_1$

   The sponsor made a strong assumption of zero or equal period effect. The methods in the reference-scaled average BE guidance [1] do not have the assumption of zero or equal period effect. Hence, the sponsor cannot make such assumptions. The sponsor must provide the theoretical proof for zero or equal period effect if the sponsor uses the guidance method. If the sponsor could not provide such proof, the estimator $\widehat{\mathrm{D}}_1$ is not an unbiased estimator which cannot be used to analyze the crossover design.

4. Partial data used in the sponsor's estimators $\widehat{\mathrm{D}}_{1\mathrm{B}}$ *and* $\widehat{\mathrm{D}}_{1\mathrm{C}}$

   The sponsor removed cells from the study design, which is not acceptable because such a modification is a way of manipulating data which will result in a favorable analysis comparing to the analysis using all the data.

5. An infinite number of unbiased estimates for the mean difference: $\mu_T - \mu_R$

   There are infinite unbiased estimators from this design and $\widehat{\mathrm{D}}_{1\mathrm{C}}$ is only one of them. In order to find the unbiased estimator $\widehat{D}$, we need to assign weights on the cells. We have the following formula,

$$\widehat{D} = \frac{1}{a_{15}+a_{21}+a_{32}+a_{35}+a_{41}+a_{44}} \begin{bmatrix} +(a_{15}\bar{y}_{15} - a_{11}\bar{y}_{11} - a_{14}\bar{y}_{14}) \\ +(a_{21}\bar{y}_{21} - a_{22}\bar{y}_{22} - a_{25}\bar{y}_{25}) \\ +(a_{32}\bar{y}_{32} + a_{35}\bar{y}_{35} - a_{31}\bar{y}_{31} - a_{34}\bar{y}_{34}) \\ +(a_{41}\bar{y}_{41} + a_{44}\bar{y}_{44} - a_{42}\bar{y}_{42} - a_{45}\bar{y}_{45}) \end{bmatrix}$$

$$= \frac{1}{a_{15}+a_{21}+a_{32}+a_{35}+a_{41}+a_{44}} \begin{bmatrix} -a_{11}\bar{y}_{11} & & -a_{14}\bar{y}_{14} & +a_{15}\bar{y}_{15} \\ +a_{21}\bar{y}_{21} & -a_{22}\bar{y}_{22} & & -a_{25}\bar{y}_{25} \\ -a_{31}\bar{y}_{31} & +a_{32}\bar{y}_{32} & -a_{34}\bar{y}_{34} & +a_{35}\bar{y}_{35} \\ +a_{41}\bar{y}_{41} & -a_{42}\bar{y}_{42} & +a_{44}\bar{y}_{44} & -a_{45}\bar{y}_{45} \end{bmatrix}$$

$$\mathrm{E}\left[\widehat{D}\right] = \mu_T - \mu_R - \frac{1}{2}(c_1 - c_2)$$

   To determine the weights, we just need to solve the following equations,

$$-a_{11} - a_{14} + a_{15} = 0$$
$$a_{21} - a_{22} - a_{25} = 0$$
$$-a_{31} + a_{32} - a_{34} + a_{35} = 0$$

$$a_{41} - a_{42} + a_{44} - a_{45} = 0$$
$$-a_{11} + a_{21} - a_{31} + a_{41} = 0$$
$$-a_{22} + a_{32} - a_{42} = 0$$
$$-a_{14} - a_{34} + a_{44} = 0$$
$$a_{15} - a_{25} + a_{35} - a_{45} = 0$$

Since there are night equations and fourteen variables, the system of equations has infinitely many solutions.

Not all the estimators from this design can be between 80%-125%. For example, if we chose weights for the cells as follows,

$$\begin{bmatrix} -\bar{y}_{11} & & -6\bar{y}_{14} & +2\bar{y}_{15} \\ +3\bar{y}_{21} & -1\bar{y}_{22} & & -2\bar{y}_{25} \\ -3\bar{y}_{31} & +11\bar{y}_{32} & -9\bar{y}_{34} & +1\bar{y}_{35} \\ +1\bar{y}_{41} & -10\bar{y}_{42} & +10\bar{y}_{44} & -\bar{y}_{45} \end{bmatrix}.$$

For the end point AUC, the mean difference $\bar{\mu}_T - \bar{\mu}_R$ is -0.2828571. The geometric mean ratio is 0.7536274, which is lower than 0.80. Hence, the bioequivalence cannot be concluded.

6. Food effect data used in the sponsor's estimator $\widehat{D}_{1D}$

   The sponsor kept all the cells in the original study design and derived an unbiased estimator. In FDA IR, we suggested the sponsor use all data for model fit in order to estimate the period effect and variability, etc. We did not ask the sponsor to use the food effect for estimating the contrast between the test product and reference product. Indeed, the contrast should not use any data from $\mathbf{Trt_3}$ (food effect). It is not acceptable to estimate the contrast using data from food effect between test and reference.

7. No proper formula for calculating the confidence interval for $(\mu_T - \mu_R)^2 - \theta\sigma_{WR}^2$ There is no proper formula for calculating the confidence interval for , where σ_{WR}^2 is the within-subject variation for the sponsor's estimators $\widehat{D}_{1E}$ and $\widehat{D}_{1F}$.

1.5 Conclusion and recommendation

In conclusion, the original crossover design is uninterpretable and the WC3079 and Asacol responded differently. The bioequivalence cannot be concluded due to the following reasons. First, the proposed estimators will not make up for the deficiency of the design. We found one unbiased estimator using weight different the sponsor's weight, whose point estimate is smaller than 0.8. Second, there are no proper statistical methods for calculating the confidence interval for $(\mu_T - \mu_R)^2 - \theta\sigma_{WR}^2$. Third, there are more cases with the small number of nonzero concentrations (≤3) for the reference product than those for the test product and the point

estimate of μ_T / μ_R for nonzero group is 0.72. Therefore, the test product WC3097 and reference product Asacol are not bioequivalent.

Reference:

1. Draft Guidance on Progesterone.

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/s/

ZHUANG MIAO
07/31/2015

MEIYU SHEN
07/31/2015

YI TSONG
08/03/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204412/ S-006	Submission Dates: 11/11/2014, 02/26/2015, 05/28/2015, 06/24/2015, 07/13/2015
Brand Name	Delzicol
Generic Name	Mesalamine
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	DCPIII
OND Division	DGIEP
Sponsor	Warner Chilcott Company LLC
Submission Type; Code	Pediatric Efficacy Supplement
Formulation; Strength(s)	Delayed Release Capsules 400 mg (Four 100-mg delayed release tablets in capsule)
Indication	Mildly to Moderately Active Ulcerative Colitis (UC) in adults and pediatric patients aged 5 years of age and older (Added age range: 5-11 years)
Pediatric Dosing Regimen	• Pediatric Patients ≥ 5 years of age: Total daily dose is weight-based up to a maximum of 2.4 grams/day with or without food (see table below); twice daily dosing for 6 weeks

Weight Group (kg)	Daily Dose (mg/kg/day)	Maximum Daily Dose (grams/day)
17 to <33	36 to 71	1.2
33 to <54	37 to 61	2.0
54 to 90	27 to 44	2.4

Table of Contents

1 Executive Summary

1.1 Recommendation

The application has been reviewed by the Office of Clinical Pharmacology and found to be acceptable from a clinical pharmacology perspective provided that a mutual agreement on label language can be reached between the sponsor and Agency.

1.2 Postmarketing Studies: None

1.3 Regulatory Background

(A) Approved Delzicol Capsules 400 mg (WC3045): NDA 204412 for Delzicol (mesalamine 400 mg delayed release) capsules were initially approved on February 1, 2013. This formulation was intended to replace Asacol 400 mg delayed release tablets, due to a potential safety concern with the plasticizer in Asacol coating (dibutylphthalate). The clinical program for Delzicol Capsules (WC3045) consisted of one reference-scaled bioequivalence study (Study PR-08210) to demonstrate bioequivalence of Delzicol capsules 400 mg to Asacol tablets 400 mg. In the approval letter, the Agency waived pediatric study requirements for children 0 to less than 5 years and deferred submission of PREA required pediatric studies in children aged 5 to 17 years.

Subsequently, FDA approved use of Asacol tablets 400 mg in pediatric patients down to 5 years of age for mildly to moderately active ulcerative colitis. Based on the established bioequivalence to Asacol tablets, Delzicol capsules received the same indication on April 28, 2014 but only in patients aged 12 years and older because WC3045 was not considered an age-appropriate formulation for patients < 12 years of age.

(B) Proposed Delzicol Capsules 400 mg (WC3079): To fulfill the PREA requirement for the approved Delzicol capsules, sponsor has developed a new delayed release formulation (phthalate-free just like the original Delzicol), also referred to as WC3079. This proposed capsule formulation contains four 100-mg tablets. Patients may either swallow the capsule intact or, in case of swallowing difficulties (particularly in younger children), open the capsule and swallow the individual 100 mg tablets. Note that the proposed WC3079 capsule is a clear, uncolored capsule printed with 'WC 400mg' in black ink containing four reddish-brown coated round tablets. Thus, the proposed Delzicol capsules differ in appearance from the approved Delzicol capsules. After the approval of WC3079, the sponsor plans to stop manufacturing WC3045.

To support the approval of the proposed Delzicol formulation in UC patients aged 5 years and older, the sponsor submitted a relative bioavailability study PR-07513

(WC3079 versus Asacol 400 mg) conducted in healthy adult subjects and a swallowability study PR-00514 (using placebo formulation) conducted in pediatric subjects 5 to 11 years of age. This review focuses on the bioavailability study (Study PR-07513) only.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Bioavailability Study (Study PR-07513):

The objectives of the study were to assess the bioavailability of the proposed Delzicol Capsules 400 mg relative to the approved Asacol Tablets 400 mg under fasted conditions as well as the food effect for the former. Due to the high variability of mesalamine pharmacokinetics, the sponsor utilized a reference-scaled bioequivalence approach and conducted a 4-sequence, 5-period, crossover study, which is not in alignment with the study designs recommended for reference scaled BE analyses of highly variable drugs (see OGD draft progesterone guidance in this regard).

In the data analyses, the sponsor eliminated treatments that were not relevant to the particular analysis in question and renumbered the study periods. This data handling assumed absence of period effects. The sponsor concluded that all PK parameters (Cmax, AUC8-48h, & AUC0-tld) met the BE criteria using the reference-scaled BE methodology. Advised by DBVI, the sponsor subsequently provided additional analyses to derive unbiased estimates of relative bioavailability without discarding any of the test or reference replicate treatment data. However, DBVI concluded that the study design and data features render it impossible to apply appropriate statistical methods to assess the relative bioavailability. Please refer to the review by Dr. Zhuang Miao dated 8/3/15.

As such, we examined various aspects of the study and conducted further analyses of the data. These included one analysis using PK data from fasted periods for sequences (Sequences #C & D) that had the fed treatment on the same study period (i.e., Period 3) without renumbering the periods. Using the reference-scaled BE testing, all PK parameters met the BE criteria. We concluded that the bioavailability of the proposed Delzicol Capsules 400 mg is comparable to that for the Asacol Tablets 400mg because of the reasons listed below. Note that for future studies, sponsors should adhere to the balanced, fully or partially replicated study designs to avoid the above statistical issues.

1. The sponsor's analysis using PK data for all treatments under fasted conditions assuming no period effect and the reviewer's analysis using data from Sequences C and D (or Sequences 3 and 4) showed that the proposed Delzicol formulation met the reference-scaled bioequivalence testing criteria. The washout period of 7 days in the study was long enough to avoid carry-over effect between study periods based on the elimination half-life of mesalamine. Therefore, the assumption of no period effect is considered reasonable.

2. We did not exclude subjects with no or low systemic exposure from the bioequivalence analyses. Rather, these data were included in the analyses as part of the PK variability. This is because most subjects with zero exposure in one study period had high concentrations when the same dosage form was given in another period.

3. The proposed Delzicol Capsules 400 mg is not bioequivalent to the approved Delzicol Capsules 400 mg. According to ONDQA/Biopharm, the dissolution testing at pH 6.5 failed the f2 test, which is part of the BE testing for mesalamine delayed-release products. However, this does not preclude the approval of the proposed product because the individual dissolution data showed that more dosage units of Asacol tablets dissolved at pH 6.5 compared to the proposed product although both formulations were designed to release drug at pH 7 and above.

Conclusion: By establishing the comparable bioavailability between the proposed product and Asacol Tablets, the pediatric indication approved for Asacol Tablets may be extended to the proposed product (WC3079). Regarding food effect, a high fat meal increased the mesalamine systemic exposure by approximately 30-45% following administration of the proposed product. This is similar to what was observed for the approved Delzicol Capsules (WC3045). As such, the proposed product can be administered without regard to food.

2 Review of Study PR-07513

"A Study to Assess the Relative Bioavailability and the Effect of Food of a New Delayed-Release Mesalamine Formulation (WC3079-19F) in Healthy Volunteers, Study PR-07513"

Study objectives:

- To assess the relative bioavailability of the proposed formulation (WC 3079-19F; over-encapsulated 4 x 100 mg delayed release, DR tablets), as compared to Asacol DR tablets, 400 mg
- To assess the effect of food on the bioavailability of mesalamine from the proposed DR formulation (WC3079-19F, 400 mg)

Study design:
Single center, open-label, randomized, single dose, replicate treatment, 5-period, 4-sequence, 2-formulation crossover study in N = 160 healthy male and female volunteers.

Subjects:
One hundred and forty-six healthy subjects completed the study, and 14 subjects 4 discontinued prematurely. Reasons for premature withdrawal from the study were: subject withdrew consent (6 subjects), AE (4 subjects), positive cotinine or drug test

result (2 subjects), and other reason (2 subjects, 1 for personal reasons and 1 for lack of compliance/reliability).

Treatments:
Treatments and treatment sequences are as shown below. All treatments were administered with 240 mL water, after overnight (at least 10 h) fasting (except treatment 3), with 7-days between treatment administrations. As the intra-subject variability of mesalamine PK is very high, a reference-scaled bioequivalence approach has been used by the sponsor (this approach was also used in the original approval of Delzicol 400 mg DR tablet (encapsulated) and in the food-effect PK study for Delzicol capsule).

Treatment 1: One Asacol (mesalamine) delayed-release tablet, 400 mg (fasted)
Treatment 2: One mesalamine delayed-release capsule (WC3079-19F); 400 mg (fasted)
Treatment 3: One mesalamine delayed-release capsule (WC3079-19F); 400 mg with food
Subjects were randomly assigned to one of the following 4 treatment sequences:
Sequence A: Treatment 1 – Treatment 3 – Treatment 2 – Treatment 1 – Treatment 2
Sequence B: Treatment 2 – Treatment 1 – Treatment 2 – Treatment 3 – Treatment 1
Sequence C: Treatment 1 – Treatment 2 – Treatment 3 – Treatment 1 – Treatment 2
Sequence D: Treatment 2 – Treatment 1 – Treatment 3 – Treatment 2 – Treatment 1

Food-effect component:
At 30 minutes prior to dosing, subjects randomized to receive one WC3079 (mesalamine) delayed-release capsule, 400 mg with food (Treatment 3) were given a high-fat (approximately 50% of total caloric content of the meal), high calorie (800 to 1000 calories) breakfast. The meal ended within 5 minutes prior to dose administration.

PK sampling:
Blood samples were collected at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 30, 36, 48, and 72 hours post-dose. All samples were stored at -70°C or colder pending shipment for assay.

Analytical method:

Plasma mesalamine concentrations were determined using a validated liquid chromatography with tandem mass spectrometry method; the bioanalytical work was performed by (b) (4)

The assay method had a lower quantification limit of 2 ng/mL. Dilution integrity was demonstrated for a 25-fold dilution. Precision (% CV) for the calibration standards ranged from 2.43 % to 3.17 %, while precision for the quality controls ranged from 3.67 % to 4.07 %. Accuracy (% RE or bias) ranged from -2.22 % to 2 % for calibration standards, and 0.5 % to 8.83 % for quality controls. The method was linear with R^2 value of 0.9993. No interfering peaks were noted at the expected retention time of the analyte or internal standard. Overall mean recovery of mesalamine at 25, 600 and 1200 ng/mL was 90.3 %, 125 % and 102 %, respectively. Stability of mesalamine was demonstrated to be 92 days at -70^{o}C, and 378 days at -80^{o}C in K2 EDTA human plasma. Stability was shown over four freeze-thaw cycles. No matrix interference was noted. Acceptance

criteria were met for incurred sample reanalysis as (b) (4) % of ISR samples had results within (b) (4) % of their mean value.

PK analyses:

PK parameters calculated for mesalamine using non-compartmental analyses are listed below. In previous discussions and Delzicol submissions, Cmax, AUC8-48h and AUC0-tldc were identified as primary criteria for reference-scaled BE analyses.

Pharmacokinetic parameter	Definition
Cmax	Maximum plasma concentration
tmax	Time of the maximum measured plasma concentration. If the maximum value occurred at more than 1 time point, tmax was defined as the first time point with this value
AUC8–48	The area under the plasma concentration (AUC) versus time curve, from 8 hours to 48 hours postdose or to the last determinable concentration (tldc), as calculated by the linear trapezoidal method
AUC0–tldc	AUC from 0 hours to the last determinable concentration (tldc), as calculated by the linear trapezoidal method
AUC0-inf	The AUC from time 0 to infinity, calculated as the sum of AUC0–tldc plus the ratio of the last measurable plasma concentration to the terminal phase rate constant.
kel	Terminal phase rate constant
t½	Terminal phase half-life = 0.693/kel
AUC%extrap	100* (1- (AUC0-tldc/AUC0-inf))

Statistical methods:

Per the sponsor, "pharmacokinetic data from subjects who completed both Treatment 1 (reference) and Treatment 2 (test) replicate treatments were included in the relative bioavailability assessment. Pharmacokinetic data from subjects who completed both Treatment 2 (reference) replicate treatments and Treatment 3 (with food; test) were included in the food effect assessment. The point estimates of the Test/Reference geometric mean ratio for Cmax, AUC8-48, and AUC0-tldc were calculated for each study objective. For Cmax, AUC8-48, and AUC0-tldc, the within-subject standard deviation for each formulation was estimated from the analysis of variance of the log-transformed parameter using the reference-scaled average bioequivalence procedure as described in the February 2011 Draft Guidance on Progesterone. The same procedure was used to determine the 95% (1-sided) upper confidence bound on the linearized criterion for these pharmacokinetic parameters".

Results:

PK parameters generated by the sponsor could be replicated by reviewer using non-compartmental PK analyses of the sponsor-provided mesalamine plasma concentration-time data (Pharsight Phoenix).

Table: Arithmetic mean (SD), and geometric mean data for key pharmacokinetic parameters (N=146)

Arithmetic Mean (SD) Geometric Mean	C_{max} (ng/mL)	$AUC_{8\text{-}48h}$ (ng h/mL)	AUC_{tldc} (ng h/mL)	Tlag (h)	Tmax (h) Mean/Median
Reference R1	159 (337) 55.4	882 (803) 453	1083 (1021) 531	8.1 (4.7)	17.6 (12.7)
Reference R2	157 (286) 63.6	889 (670) 352	1144 (955) 644	7.7 (4.8)	16.6 (11.7)
Test T1	207 (323) 78.6	701 (620) 487	1035 (987) 667	6.2 (4.3)	13.6 (11.5)
Test T2	201 (422) 60.6	712 (866) 445	1007 (1222) 574	6.8 (4.3)	15.4 (13.0)
Test with food, F	214 (320) 90.8	948 (853) 679	1128 (974) 780	9.9 (4.1)	17.6 (11.1)

Sponsor's bioequivalence analysis:

The sponsor used reference-scaled BE methodology to analyze the BE data. In the analyses, matching sequences were collapsed after removal of food-effect treatment 3 from each sequence as shown in the schematic below, which resulted in 2 sequences rather than the original 4 and that geometric mean and ratio estimates were based on patients with no missing values for the 2 test and 2 reference variables.

	Period p_j				
Sequence g_i	1	2	3	4	5
1	Trt_1	~~Trt_3~~	Trt_2	Trt_1	Trt_2
2	Trt_2	Trt_1	Trt_2	~~Trt_3~~	Trt_1
3	Trt_1	Trt_2	~~Trt_3~~	Trt_1	Trt_2
4	Trt_2	Trt_1	~~Trt_3~~	Trt_2	Trt_1

Trt_1 = Asacol, fasted; Trt_2 = Delzicol, fasted; ~~Trt_3 = Delzicol, fed~~

The sponsor concluded bioequivalence of the proposed Delzicol formulation to the approved Asacol formulation as for all three key PK parameters tested (i.e., Cmax, AUC8-48 and AUC0-tldc) the 95% upper confidence bounds of the linearized criterion were < 0, and the point estimates of the Test/Reference geometric mean ratio were within 80.00 and 125.00%.

		Within-Subject SD (%CV)		Geometric Mean (LSM)		Ratio (%)	95% Upper Bound of the Linearized
PK Parameter	N	Test	Reference	Test	Reference	(T / R)	Criterion
Cmax	146	1.20 (179)	1.31 (214)	68.9	59.4	115.96	-1.11
AUC8-48	146	0.739 (85.2)	1.52 (301)	465	484	96.07	-1.54
AUC0-tldc	146	0.833 (100)	1.52 (301)	618	586	105.52	-1.53

Cmax = Maximum plasma concentration (ng/mL);
AUC8-48 = AUC from time 8 hours to 48 hours (ng·h/mL);
AUC0–tldc = AUC from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)
Test(T) = WC3079 capsule fasted; Reference(R) = Asacol tablet fasted.
Ratio = The ratio of geometric means.
PK = Pharmacokinetic; SD = standard deviation; %CV=100*sqrt(exp(SD**2)-1); LSM = least squares mean from ANOVA model.

The above analyses involved elimination of fed period, which assumed absence of period effects. In contrast, the two designs (full and partial replicated, respectively) recommended in the OGD draft guidance (as shown below) do not require any assumptions on period effect.

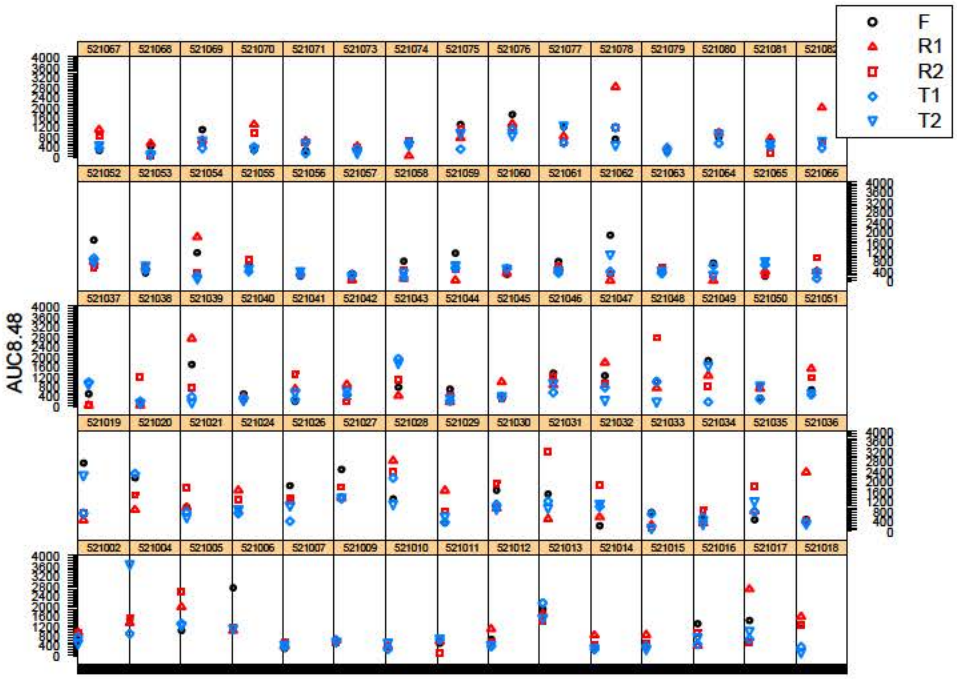
Trt_R = Reference treatment; Trt_T = Test treatment

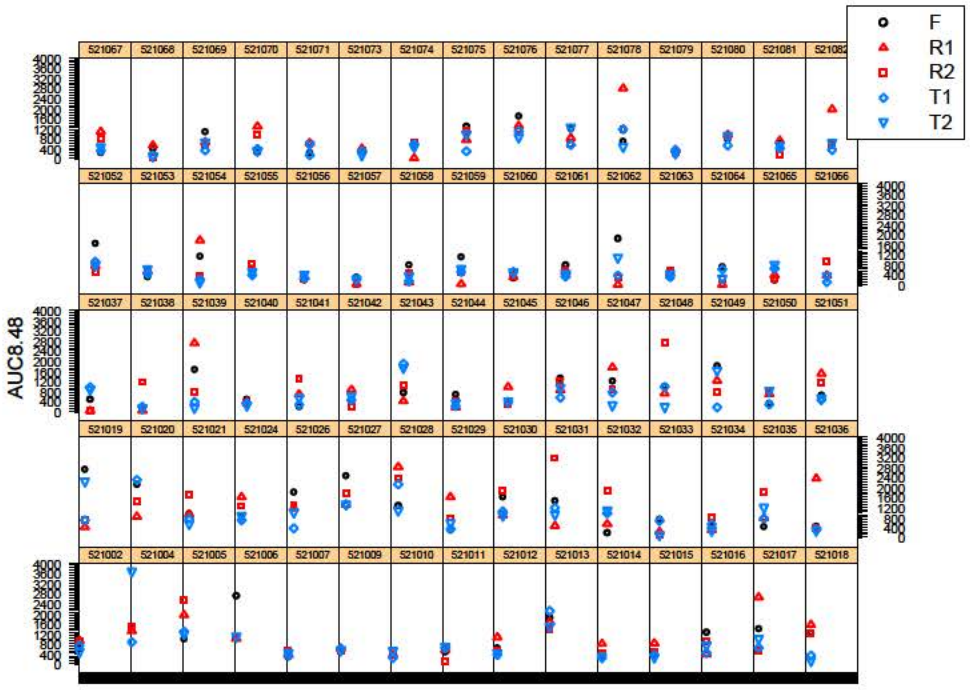
	Period p_j			
Sequence g_i	1	2	3	4
1	Trt_T	Trt_R	Trt_T	Trt_R
2	Trt_R	Trt_T	Trt_R	Trt_T

	Period p_j		
Sequence g_i	1	2	3
1	Trt_T	Trt_R	Trt_R
2	Trt_R	Trt_T	Trt_R
3	Trt_R	Trt_R	Trt_T

Thus, on the advice of statisticians from the Office of Biometrics, DBVI, the sponsor conducted additional analyses to identify unbiased estimates of the relative bioavailability. Subsequently, DBVI determined that the study design is uninterpretable and the WC3079 and Asacol responded differently. The following are DBVI comments provided in their review: "The bioequivalence cannot be concluded due to the following reasons: First, the proposed estimators will not make up for the deficiency of the design. We found one unbiased estimator using weight different the sponsor's weight, whose point estimate is smaller than 0.8. Second, there are no proper statistical methods for calculating the confidence interval for $(\mu_T - \mu_R)^2 - (\theta\sigma_{WR})^2$. Third, there are more cases with the small number of nonzero concentrations ($\leq$3) for the reference product than those for the test product and the point estimate of μ_T / μ_R for nonzero group is 0.72. Therefore, the test product WC3097 and reference product Asacol are not bioequivalent."

Individual subject $AUC_{8\text{-}48}$ data by treatment/replicate:





*subject IDs [redacted] (b) (6) had at least one value exceeding 4000 and therefore that data is not seen in the plots above

Examination of observed zero exposures (Reviewer's analysis):

Fifteen subjects in the reference group and 2 in the test group (1 common subject) had all zero concentrations throughout the 72 hour sampling window. For the purpose of statistical analyses, the sponsor assigned a value of 1 to Cmax and AUC parameters. The following table shows AUC_{8-48} data for each of these patients across the treatments and for the replicates within treatments (C_{max} and AUC_{tldc} were similarly assigned value of 1 in presence of zero concentrations and hence not shown here). Since these are observed values, reviewer agrees that data should be included in the analyses and not deleted as outliers.

Data shows that for the majority of individuals, the zero concentrations were noted in only one of the two replicates of test or reference treatments. This demonstrates the intra-subject, intra-occasion variability of mesalamine plasma pharmacokinetics. In addition, the new formulation (test) had fewer instances of zero concentrations so there is less concern on this issue. It is likely (although cannot be conclusively proven) that presence of four individual 100 mg units in the new capsule formulation would reduce the incidence of complete product failure to release drug in the colon, as opposed to having one unit as in the reference formulation.

ID (b) (6)	**R1** AUC_{8-48}	**R2** AUC_{8-48}	**T1** AUC_{8-48}	**T2** AUC_{8-48}
	1	5.1	936.4	801.2
	1	1134	158	59.3
	1	275	365	1018
	1	223	604.4	195.5
	1	623	557	405
	1	684	260	445
	1	825	1077	450
	1	812	369	12.8
	1	1147	326	1416
	30.2	1	213	156
	958	1	162	416
	456	1	572	289
	791	1	16.3	213
	422	1	69	206
	691	1	2	1
	969	387	1	43

Additional Bioavailability analyses by Reviewer:

We utilized only the data from sequences 3 and 4 above (or C and D per original study design) to run the BE analyses. In both these sequences, food-effect treatment 3 was placed in the third period and therefore discounting this period from both these sequences

prior to analyses would have a similar effect on both Test and Reference formulations and no renumbering of periods was necessary.

Sequence C: R1 – T1 – Fed- R2 – T2
Sequence D: T1 – R1 – Fed- T2 – R2
where, Reference (R1 &R2) is the reference Asacol tablets 400 mg and Test (T1 & T2) is the proposed Delzicol capsules 400mg.

Using this data set, statistical analyses were conducted again using SAS 9.3 which generated the following output, suggesting that all three key PK parameters passed the BE criteria:

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
$LAUC_{TLDC}$	0.92	.	.	2.6431803	1.6257861	-1.636809	Scaled/PE	PASS
$LAUC_{8-48}$	0.87	.	.	2.6813033	1.6374686	-1.642708	Scaled/PE	PASS
LCMAX	0.97	.	.	1.8334341	1.3540436	-1.142678	Scaled/PE	PASS

Food-effect on PK:

The second objective of the present study was to assess the food effect on the PK of mesalamine from the new Delzicol (WC3079) formulation. Thus, the PK of mesalamine after the proposed formulation is administered under fed and fasted conditions were compared to estimate the magnitude of any food-effect on absorption. This again, involved assumptions related to absence of period effects, and collapsing of identical sequences (3 and 4 below) in the original analyses.

	Period p_j				
Sequence g_i	1	2	3	4	5
1	~~Trt_1~~	Trt_3	Trt_2	~~Trt_1~~	Trt_2
2	Trt_2	~~Trt_1~~	Trt_2	Trt_3	~~Trt_1~~
3	~~Trt_1~~	Trt_2	Trt_3	~~Trt_1~~	Trt_2
4	Trt_2	~~Trt_1~~	Trt_3	Trt_2	~~Trt_1~~

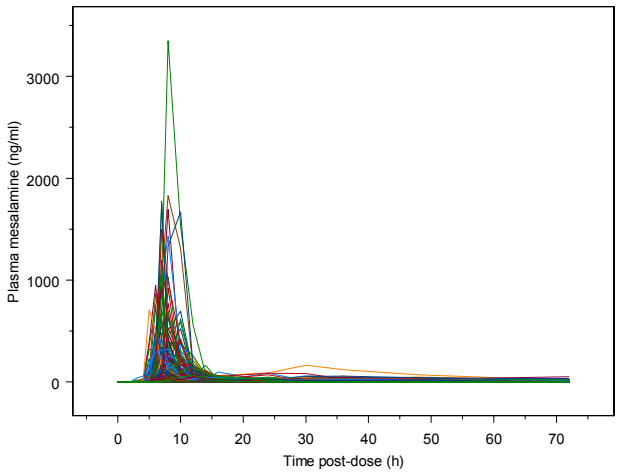
~~Trt_1 = Asacol, fasted~~; Trt_2 = Delzicol, fasted; Trt_3 = Delzicol, fed

The results from this original food effect analyses are shown below and suggest an increase in Cmax, AUC8-48 and AUCtldc by 32 %, 46 % and 29 %, respectively when administered with a high fat meal:

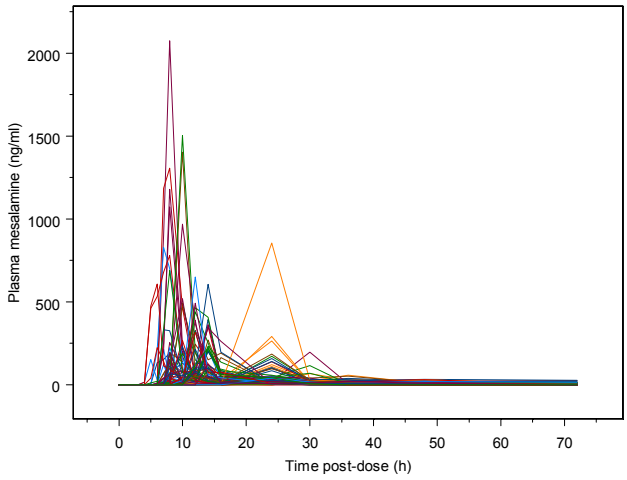
		Within-Subject SD (CV%)		Geometric Mean (LSM)		Ratio (%)	95% Upper Bound of the Linearized
PK Parameter	N	Test	Reference	Test	Reference	(T / R)	Criterion
Cmax	146	NA	1.20 (179)	91.1	69.0	132.11	-0.825
AUC8-48	146	NA	0.738 (85.1)	681	466	146.22	-0.152
AUC0-tldc	146	NA	0.831 (99.7)	802	620	129.39	-0.354
AUC0-inf	99	NA	0.575 (62.6)	1227	1087	112.90	-0.183

Cmax = Maximum plasma concentration (ng/mL);
AUC8-48 = AUC from time 8 hours to 48 hours (ng·h/mL);
AUC0–tldc = AUC from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)
Test(T) = WC3079 capsule with food; Reference(R) = WC3079 capsule fasted.
Ratio = The ratio of geometric means. NA = not applicable
BE = Bioequivalence; SD = standard deviation; CV%=100*sqrt(exp(SD**2)-1); LSM = least squares mean from ANOVA model

Fasted- New formulation



Fed- new formulation



3 Labeling Comments:

- The PK parameters for the new Delzicol product should be reflected in the label.
- The label should indicate that the proposed product can be administered with or without food.

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/s/

SUE CHIH H LEE
08/12/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s006

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D.
Division of Pediatric and Maternal Health,
Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Pediatric Team Leader,
Division of Pediatric and Maternal Health,
Office of New Drugs

Linda Lewis, M.D., Acting Deputy Director,
Division of Pediatric and Maternal Health,
Office of New Drugs

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Delzicol (mesalamine) Delayed-Release Capsule, 400 mg

Application number: NDA 204412 (IND 26093)

Re: Input on labeling and PREA requirements

Sponsor: Warner Chilcott, LLC

Approved indications:

- Treatment of mildly to moderately active ulcerative colitis in patients 12 years of age older
- Maintenance of remission of ulcerative colitis in adults

Dosage form and Route of administration: 400 mg delayed-release capsule administered orally

Approved dosing regimen: **For the treatment of mildly to moderately active ulcerative colitis:**

- Adults: 800 mg three times daily with or without food (2.4 grams/day) for 6 weeks
- Pediatric Patients 12 years or older: Total daily dose is weight-based up to a maximum of 2.4 grams/day with or without food (see table below); twice daily dosing for 6 weeks

Weight Group (kg)	Daily Dose (mg/kg/day)	Maximum Daily Dose (grams/day)
17 to <33	36 to 71	1.2
33 to <54	37 to 61	2.0
54 to 90	27 to 44	2.4

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

Two Delzicol 400 mg capsules have not been shown to be bioequivalent to one Asacol HD (mesalamine) delayed-release 800 mg tablet.

Proposed indication: Treatment of mild to moderately active ulcerative colitis (UC) in patients 5 years and older.

Proposed dosage form and Route of administration: 400 mg delayed-release capsule administered orally. Each capsule contains four coated 100 mg mesalamine tablets. *Reviewer comment: This dosage form is the sponsor's proposed age-appropriate formulation consisting of a capsule containing four 100 mg tablets.*

Proposed dosing regimen:
Same as approved with the following additional instructions:
Do not crush, break, or chew the capsules. Swallow whole capsule (b) (4) or open capsule carefully, then swallow the content (tablets) (b) (4)

Consult Request:
DGIEP requested DPMH review proposed labeling for this efficacy supplement, and review study (PR-00514) that was conducted in healthy children using prototype capsules containing four 100 mg placebo tablets to determine if the proposed dosage form is an age appropriate product for children at age of 5 years and older.

Materials Reviewed:

- Meeting Package from sponsor (November 12, 2014)

- DPMH consult review on Delzicol (formerly known as WC3045) (mesalamine) 400 mg delayed-release capsules, NDA 204412 (January 30, 2013 [DARRTS reference ID 3249805], September 19, 2013 [DARRTS reference ID 3373178] and March 4, 2014 [DARRTS reference ID 3463860])
- Sponsor's proposed Delzicol (mesalamine) 400 mg delayed-release capsule labeling, NDA 204412 (November 12, 2014,)
- Current Delzicol (mesalamine) 400 mg delayed-release capsule label (October 27, 2014) from Drugs@FDA

Background:
Delzicol (mesalamine) 400 mg capsule, is a locally acting, phthalate-free, delayed-release aminosalicylate indicated for the treatment of mildly to moderately active Ulcerative Colitis (UC) in patients 12 years and older and for the maintenance of remission of UC in adults. Delzicol was initially approved on February 1, 2013 based on demonstration of bioequivalence to the reference listed drug, Asacol (mesalamine, NDA 19651) via a comparative adult pharmacokinetic (PK) study, in addition to comparative dissolution studies. Asacol is a locally acting, delayed-release aminosalicylate, initially approved in January, 1992, and indicated for the treatment of mild to moderately active UC in patients 5 years and older and maintenance of remission of mild to moderately active UC in adults. Asacol contains dibutyl phthalate (DBP), an excipient associated with potential adverse reproductive and fetal developmental effects. Delzicol was formulated without DBP to replace Asacol. Note that Warner Chilcott, LLC is the sponsor for Asacol, Asacol HD and Delzicol. For further background information on Delzicol, Asacol and Asacol HD, see DPMH's prior consult reviews on Delzicol (mesalamine) 400 mg delayed-release capsules, NDA 204412 dated January 30, 2013; September 19, 2013 and March 4, 2014.

Upon initial approval of Delzicol, the following pediatric postmarketing requirements (PMRs) were issued under the Pediatric Research and Equity Act (PREA):

2011-1 A randomized, double-blind study in pediatric patients ages 5 to 17 years with ulcerative colitis using an age-appropriate formulation to evaluate the pharmacokinetics, safety, and clinical response of pediatric patients undergoing six weeks of oral mesalamine therapy. The study should compare at least two different dose levels of mesalamine and enroll at least 40 pediatric patients in each dosing arm.
Reviewer comment: This is a study requirement to evaluate treatment (induction of maintenance) of mild to moderately active UC in pediatric patients 5 to 17 years of age.

2011-2 A randomized, double-blind study in pediatric patients ages 5 to 17 years using an age-appropriate formulation for the maintenance of remission of ulcerative colitis.

The indication for treatment (induction of maintenance) of UC was extended down to patients 12 years of age on April 28, 2014, based on studies that supported the approval

of Asacol in patients 5 years of age and older. Although these pediatric studies supported the efficacy and safety of Delzicol for induction down to patients 5 years of age, the approved Delzicol capsule is larger [i.e., size (b) (4) mm] than the Asacol 400 mg tablet [i.e., size (b) (4) mm]. Therefore, Delzicol was not deemed appropriate for patients less than 12 years of age, and the induction indication was restricted to patients 12 years of age and older. Additionally, the PREA PMR related to the treatment of UC was only partially fulfilled. Although no additional studies were necessary to fulfill this PMR, the sponsor was required to produce an age-appropriate formulation for younger patents. The PREA PMRs also remain outstanding for the maintenance indication. (See DPMH's (formerly PMHS') prior consult review on Delzicol (mesalamine) 400 mg delayed-release capsules, NDA 204412 dated January 30, 2013; September 19, 2013; and March 4, 2014 for further background information on the development of an age-appropriate formulation.)

In order to fulfill the remainder of the pediatric assessment for treatment (induction of maintenance) of UC in patients 5 to 11 years of age, the sponsor has developed a new phthalate-free age-appropriate formulation. The sponsor submitted an efficacy supplement on November 12, 2014 which includes the results of a swallowability study in patients 5 to 11 years of age, in addition to adult bioequivalence and dissolution data. The division consulted DPMH to assist in the review of the application and provide feedback on labeling for Delzicol for pediatric use,

Comments on PREA:
Under PREA, 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.

The proposed efficacy supplement does not trigger PREA because the proposed supplement would only *extend* the currently approved induction indication to pediatric patients 5 to 11 years of age, without changing the dosing regimen, and not provide a new indication for the product.

Comments on the Age-Appropriate Formulation:
The sponsor's proposed age-appropriate formulation consists of a size (b) (4) capsule ((b) (4) mm) containing four 100 mg tablets (b) (4) mm diameter/ (b) (4) mm thickness). The capsule can be opened and the smaller tablets can be swallowed whole. Of note, the Asacol formulation which is approved for patients down to 5 years of age is a (b) (4) mm tablet (see Figure 1 below).

Figure 1: Asacol 400 mg tablet ([(b) (4)] mm), Delzicol 400 mg capsule (size [(b) (4)] mm),and the sponsor's proposed 400 mg age-appropriate Delzicol formulation (size [(b) (4)] with 4 x100 mg tablets [(b) (4)] mm diameter/ [(b) (4)] mm thickness]).

The sponsor conducted a single-center, open-label, single-dose study with the proposed formulation in 60 healthy children 5 to 11 years of age to evaluate swallowability. Twenty children were enrolled in each of three cohorts: 5 to 6; 7 to 9; and 10 to 11 years of age. Each child was given two capsules containing eight total placebo tablets (four tablets in each capsule), and instructed to swallow all eight tablets within 15 minutes. The following summarizes the results:

- Overall, 42 (70%) of the children swallowed all eight tablets.
- Children 7 to 11 years:
  - 34/40 (85%) swallowed all eight tablets (two children swallowed one tablet).
  - 4/40 (10%) swallowed none of the tablets.
- Children 5 to 6 years:
  - 8/20 (40%) swallowed all eight (one child swallowed one tablet; two children swallowed two tablets).
  - 9/20 (45%) swallowed none of the tablets.
- Most children swallowed the tablets in < 5 minutes (three children swallowed one additional tablet between 5 and 10 minutes after administration).

Reviewer comment: Although the majority (45%) of 5 to 6-year-olds were unable to swallow the entire dose (all eight tablets), the swallowability study was not conducted in the proposed population of children with UC. Guidance from the Crohn's & Colitis Foundation of America[1] and the European Medicines Agency[2] advises that patients with chronic diseases can be trained on pill swallowing. Therefore, a larger percentage of young patients with UC are anticipated to be able take the proposed formulation. Furthermore, the encapsulated tablets are much smaller than currently approved Asacol tablets (even though the dose is smaller, and a greater number would need to be taken).

[1] Pill Swallowing Techniques for Kids and Teens. Crohn's & Colitis Foundation of America Fact Sheet. July 2015. http://www.ccfa.org/assets/pdfs/PillSwallowing.pdf
[2] Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use, May, 19, 2011

Therefore, the proposed formulation is acceptable for UC patients 5 years of age and older. Additionally, information on swallowability can be obtained during the required pediatric maintenance trial.

DPMH Review of labeling:
The DPMH labeling review will focus on edits to section 1 (Indications and Usage) and 8.4 (Pediatric Use).

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. When substantial evidence does not exist to support a pediatric indication, all relevant pediatric information related to the unapproved use should be restricted to the Pediatric Use subsection only, to avoid an inference of an approved pediatric indication as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. The guidance also states that any negative or inconclusive pediatric studies must be described in the Pediatric Use subsection, and the basis for the determination of safety and effectiveness in the pediatric population should also be provided (e.g., providing an explanation for why the available evidence does not support pediatric approval). (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013.)

Discussion on Labeling Recommendations:
See Appendix 1 for proposed applicant labeling for Delzicol dated November 12, 2014.

Recommendations for pediatric use labeling for Delzicol are structured after Asacol labeling. Information regarding the data used to support the pediatric indication for Delzicol should be included in the relevant sections per 21 CFR 201.57(c)(9)(iv) throughout labeling. The Indications and Usage section should state that Delzicol is indicated for the treatment of mild to moderately active UC in adults and pediatric patients 5 to 17 years of age and that the maintenance indication pertains to adults and not to pediatric patients. Additionally, the Pediatric Use subsection should state that safety and effectiveness have been established for Delzicol for treatment in patients 5 years and older, but not for treatment in patients less than 5 years of age or for maintenance in pediatric patients.

The basis used to support the pediatric indication should be outlined in the Pediatric Use subsection (e.g., extrapolation of efficacy from adequate and well-controlled studies with additional data supporting pediatric use). Additionally, the pediatric clinical trial supporting the pediatric indication should be summarized in the Pediatric Use section of Delzicol labeling with cross-references to a more detailed description in the appropriate sections of labeling. Because the pediatric studies that will be described in Delzicol

labeling were conducted using Asacol 400 mg tablets, DPMH also recommends that Delzicol labeling state that the data presented in subsection 8.4 are from studies conducted with mesalamine 400 mg delayed-release tablets. DPMH also recommends excluding a description of the swallowability study and instead discussing the study in clinical reviews.

DPMH Recommended labeling for Delzicol:

1 INDICATIONS AND USAGE

1.1 Treatment of Mildly to Moderately Active Ulcerative Colitis

DELZICOL is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

1.2 Maintenance of Remission of Ulcerative Colitis in Adults

DELZICOL is indicated for the maintenance of remission of ulcerative colitis in adults.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of DELZICOL for the treatment of mildly to moderately active ulcerative colitis in pediatric patients 5 to 17 years of age has been established based on adequate and well-controlled studies using mesalamine delayed-release 400 mg tablets. Use of DELZICOL in these pediatric age groups is supported by evidence from adequate and well controlled studies of mesalamine delayed-release 400 mg tablets in adults and a single 6-week study in 82 pediatric patients 5 to 17 years of age *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*.

The safety and effectiveness of DELZICOL for the treatment of mildly to moderately active ulcerative colitis in pediatric patients below the age of 5 years have not been established. The safety and effectiveness of DELZICOL in the maintenance of remission of ulcerative colitis in pediatric patients have not been established.

Conclusion:
DPMH agrees that the proposed formulation is appropriate for patients 5 years of age and older. Furthermore, DPMH agrees that the indication for the treatment of UC should be extended down to patients 5 years of age pending a determination that bioequivalence of the new formulation to the Asacol formulation has been established or adequate justification is provided to determine that the two formulations are sufficiently similar. DPMH also recommends that the approval letter state that the pediatric assessment for treatment of UC in patients 5 to 17 years of age has been fulfilled, but the pediatric study requirement for the maintenance of UC in patients 5 to 17 years of age also remains outstanding. Additionally, the ability of children to swallow the proposed formulation

can be further assessed in the pediatric trials required to fulfill the PREA PMRs for maintenance.

DPMH reviewed the sponsor's draft labeling, and participated in the team and labeling meetings held between November, 2014 and August, 2015. DPMH also provided assistance in preparation for the Pediatric Review Committee meeting on July 29, 2015. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

Appendix I: Proposed Applicant Labeling for Delzicol (November 12, 2014)

1 INDICATIONS AND USAGE

1.1 Treatment of Mildly to Moderately Active Ulcerative Colitis

DELZICOL® (mesalamine) delayed-release capsules are indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

1.2 Maintenance of Remission of Ulcerative Colitis in Adults

DELZICOL® (b) (4) indicated for the maintenance of remission of ulcerative colitis in adults. (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

The safety and effectiveness of (b) (4) for treatment of mildly to moderately active ulcerative colitis (b) (4) is supported by evidence from adequate and well controlled studies of mesalamine delayed-release 400 mg tablets in adults and a single (b) (4) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*. (b) (4) (b) (4)

(b) (4)

(b) (4)

The safety and effectiveness of DELZICOL in (b) (4) have not been established. The safety and effectiveness of DELZICOL in the maintenance of remission of ulcerative colitis in pediatric patients have not been established.

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/s/

ERICA D RADDEN
08/11/2015

HARI C SACHS
08/12/2015
I agree with these recommendations.

LINDA L LEWIS
08/12/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: July 28, 2015

To: Stacy Barley, RN, MSN, MSHA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204412/S006
OPDP Comments for draft Delzicol (mesalamine) delayed-release capsules, for oral use PI

OPDP has reviewed the proposed Delzicol (mesalamine) delayed-release capsules PI, retrieved from SharePoint on July 28, 2015, and have no additional comments.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MEETA N PATEL
07/28/2015

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 19, 2015
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 204412/S-06
Product Name and Strength:	Delzicol (mesalamine) delayed-release capsules 400 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Warner Chilcott
Submission Date:	November 12, 2014
OSE RCM #:	2014-2499
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Kendra Worthy, Pharm.D.

REASON FOR REVIEW

This review is in response to a request by DGIEP to review proposed prescribing information and carton labels for any areas that may cause medication errors. This pediatric supplement proposes to expand indication for the treatment of mildly to moderately active ulcerative colitis (UC) to patients 5 years of age and older with a new a phthalate free formulation of 400 mg mesalamine delayed-release capsule containing four 100 mg mesalamine tablets.

MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is currently marketing a 400 mg capsule for the treatment of mildly to moderately active ulcerative colitis in patients 12 years of age and older. Since the current formulation is not considered to be age appropriate for pediatric patients 5 year and older, the Applicant has developed a phthalate free formulation of 400 mg mesalamine delayed-release capsule containing four 100 mg mesalamine tablets. We reviewed proposed prescribing information and made the following recommendations for the Division to consider. We defer to the Division for the appropriateness of the pediatric dosing information in the label. Additionally, we did not identify any relevant medication error concerns from our search of the FAERS database, previous DMEPA reviews, and ISMP Newsletters.

4.0 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS TO THE DIVISION:

Prescribing Information

1. Consider replacing the symbols "<" and "≥" with their intended meanings in in the pediatric table in Dosing and Administration to prevent misinterpretation and confusion.

2. The dose in the same pediatric table in Dosing and Administration contains a trailing zero. Remove the trailing zero (e.g. 2 g) to avoid a ten-fold misinterpretation.

4.2 RECOMMENDATION TO WARNER CHILCOTT:

Container Label:

1. Since this is a unique formulation, i.e., a capsule that contains four tablets, it is important for patients and caregivers to clearly understand the important administration instructions. Therefore, move the important warning statements, "Swallow the capsules or tablets whole; do not cut, break, crush or chew the capsule or the tablet. The capsule may be carefully opened and the contents (tablets) can be swallowed." to the principle display panel under the strength presentation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Delzicol that submitted Warner Chilcott on November 12, 2014.

Table 2. Relevant Product Information for Delzicol

Initial Approval Date	February 1, 2013
Active Ingredient	Mesalamine
Indication	1) Treatment of mildly to moderately active ulcerative colitis in patients 5 years of age or older. 2) Maintenance of remission of ulcerative colitis in adults
Route of Administration	Oral
Dosage Form	Delayed-release capsule
Strength	400 mg
Dose and Frequency	For the treatment of mildly to moderately active ulcerative colitis: Adults: 800 mg (two 400 mg capsules) three times daily for 6 weeks. Pediatric Patients 5 years or older: Total daily dose is weight-based up to a maximum of 2.4 grams/day with or without food (see Table below); twice daily dosing for 6 weeks

Weight Group (kg)	Daily Dose (mg/kg/day)	Maximum Daily Dose (grams/day)	Morning Dosage	Afternoon Dosage
17 to <33	36 to 71	1.2	two 400 mg capsules	one 400 mg capsules
33 to <54	37 to 61	2.0	three 400 mg capsules	two 400 mg capsules
54 to 90	27 to 44	2.4	three 400 mg capsules	three 400 mg capsules

	For the maintenance of remission of ulcerative colitis in adults, 1.6 g (four 400 mg capsules) daily, in two to four divided doses
How Supplied	Bottles of 180 capsules
Storage	Room temperature
Container and Closure System:	Child-resistant cap

APPENDIX C. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 31, 2015, we searched the L: drive using the term, Delzicol, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews[1], and we confirmed that all of our previous recommendations were implemented.

[1] Calderon, M. Label and Labeling Review for Delzicol. NDA 204412. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 11 26 32 p. OSE RCM No.:2013-2251

Calderon, M. Label and Labeling Review for Delzicol. NDA 204412. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 02 01 32 p. OSE RCM No.:2013-225-1

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On March 31, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Delzicol

D.2 Results

Our search identified no case that was relevant for this review.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 31, 2015, using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	**November 1, 2013 to March 1, 2015**
Product	**Delzicol** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

E.2. Results

Our search identified three cases and two cases described error relevant for this review.

Wrong Product (n=1)

A report of a patient using Delzicol instead of Asacol HD. Patient had both medications in the cabinet and didn't notice the difference for two and a half weeks. Patient had severe pain, swelling and stiffness. No root cause was described.

Wrong Technique (n=1)

A report of a patient taking Delzicol capsule without the outer capsules shell and experiencing gastritis. No root cause was described.

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

We excluded one case because it described error unrelated to label and labeling and the other two cases described above are excluded from the overall assessment. We verified both Asacol HD label and Delzicol label and Delzicol label clearly indicates that it is not bioequivalent to Asacol HD. Additionally, the Applicants of both products are the same and they are planning to replace Asacol product line with Delzicol products. The second report of patient removing the outer capsule shell is clearly addressed on the Delzicol label by the warning statements on the principal display panel, (b) (4) (b) (4). We note that in both of these cases, the labels are adequately addressed and therefore they are excluded from the overall assessment of this supplement.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Delzicol labels and labeling submitted by Warner Chilcott submitted on May 5, 2015.

Prescribing Information
Carton and Container Labels

Trade Label:

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

12 count sample carton label

12 count sample container label


(b) (4)

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/s/

SHERLY ABRAHAM
05/19/2015

KENDRA C WORTHY
05/19/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 26, 2015

TO: Division of Gastroenterology and Inborn Errors Products (DGIEP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 204412/S-006

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

The site listed below was inspected within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

SHILA S NKAH
02/26/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 9, 2015

TO: Division of Gastroenterology and Inborn Errors Products (DGIEP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 204412/S-006

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	QPS Bio-Kinetic	1820 West Mount Vernon, Springfield, MO 65802

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/s/

SHILA S NKAH
04/09/2015