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*APPLICATION NUMBER:*

**204412Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Joyce Korvick, MD, MPH Deputy Director for Safety Division of Gastroenterology and Inborn Errors Products (DGIEP)
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	NDA 204412
<b>Applicant Name</b>	Warner Chilcott
<b>Date of Submission</b>	July 31, 2012
<b>PDUFA Goal Date</b>	February 1, 2013
<b>Proprietary Name / Established (USAN) Name</b>	Delzicol (mesalamine)
<b>Dosage Forms / Strength</b>	Delayed Release Capsule, 400 mg
<b>Route of Administration</b>	Oral
<b>Proposed Indication(s)</b>	Treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis
<b>Action/Recommended Action</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Aisha Peterson Johnson
Statistical Review	N/A
Nonclinical Pharmacology Toxicology Review	Sruthi King
CMC Review	Hitesh Shroff
ONDQA Biopharmaceutics Review	John Duan
Clinical Pharmacology Review	Sandhya Apparaju
DPDP/OPDP Review	Kathleen Klemm
DBGLPC Review	Sripal Mada
CDTL Review	Sue-Chih Lee
OSE/DMEPA Review	Denise Baugh
SEALD Review	Jeanne Delasko
PMHS Review	Jeanine Best, Erica Radden

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  
 DBGLPC = Division of Bioequivalence and GLP Compliance/Office of Scientific Investigations  
 DPDP/OPDP= Division of Professional Drug Promotion, Office of Prescription Drug Proportion.  
 DRISK=Division of Risk Management  
 CDTL=Cross-Discipline Team Leader  
 PMHS = Pediatric and Maternal Health Staff, Office of New Drugs  
 SEALD – Study Endpoints and Labeling Development

## Signatory Authority Review

### 1. Introduction

This application proposes a new formulation of mesalamine 400mg to the market. The new product, DELZICOL (mesalamine) delayed release capsules 400 mg, is intended to replace Asacol (mesalamine) delayed release tablets 400 mg. This new formulation does not include dibutyl phthalate (DBP) that is associated with safety concerns. There is evidence from animal studies showing that DBP is associated with external and skeletal malformations and adverse effects on the male reproductive system. There is no substantial human safety information available at this time.

Although the currently available human data are limited, the “Agency has determined that there is evidence that exposure to DBP ... from pharmaceuticals presents a potential risk of developmental and reproductive toxicity.”<sup>1</sup> In a recent Federal Register Notice, the Agency recommends that pharmaceutical sponsors avoid the use of DBP and di(2-ethylhexyl) phthalate (DEHP) as excipients in CDER-regulated drug and biologic products.

Dibutyl phthalate is an inactive excipient in Asacol’s enteric coating. The human daily intake of DBP based on the maximum recommended dose of Asacol tablets is about 21 mg.

The estimated Maximum daily exposure of DBP (6 Asacol tablets per day) is calculated to be 0.35mg/kg/day based upon 60 kg body weight. It would be higher for pediatric patients whose weight is much lower than 60 kg. These exposures are higher than those recommended by the EPA (0.1 mg/kg/day) and the European Food Safety Authority (EFSA) tolerable daily intake limit (0.01 mg/kg/day).

As a result of these findings, the Division of Gastroenterology and Inborn Errors Products (DGIEP) determined it was prudent to change the professional labeling of Asacol to provide information on the effects of DBP in animals and humans, as well as requiring the sponsor to reformulate their product without DBP. DGIEP requested that Warner Chilcott revise labeling to add information regarding DBP, especially in the Pregnancy and Nursing Mothers section of labeling (September 17, 2009). Because there are other mesalamine products on the market, this information would permit physicians and patients to select other products that do not contain DBP based upon their perception of the risk. The FDA also requested that Warner Chilcott develop a new formulation without DBP. NDA 204412 contains data supporting the reformulated mesalamine 400 mg delayed-release capsule formulation. Delzicol includes dibutyl sebacate (DBS) instead of DBP as the plasticizer in its enteric coating. Delzicol is an over-encapsulated tablet and contains the same release-controlling excipient Eudragit S as in the approved Asacol delayed release 400 mg tablets.

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<sup>1</sup> December 2012, Federal Register Notice. Limiting the Use of Certain Phthalates and Excipients in CDER-Regulated Products.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm330792.htm>

## 2. Background

Asacol (mesalamine) is approved for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis in adults. The safety and effectiveness have not been determined in pediatric patients. (NDA 19651; originally approved 1992). This is a 505(b)(1) application. The proposed indications and dosing regimens are the same as those for Asacol tablets; the treatment of mild to moderately active ulcerative colitis (800 mg TID) and for the maintenance of remission of ulcerative colitis (1.6 g daily, in divided doses), for adults only. The safety and effectiveness of Asacol has not been established in children. No new safety and or efficacy trials were conducted by the Applicant using the proposed capsule product. The Applicant submitted a comparative pharmacokinetic study and comparative dissolution studies to establish bioequivalence of the proposed product to the reference product: Asacol delayed release tablets 400 mg. This application was given a 6 month priority review designation because of the safety issue.

The exact mechanism of action of mesalamine is unknown, but it has been suggested to be topical rather than systemic. 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.

The marketed tablets are enteric coated so that the active ingredient is released at pH greater than 7, found in the terminal ileum and beyond, to provide topical mesalamine exposure in the colon.

### **Regulatory History:**

Tracked Safety Issue #771 was opened September 1, 2009 to address the presence of dibutyl phthalate in the delayed release coating of Asacol 400 mg and Asacol HD tablets. At that time Proctor and Gamble was the sponsor. Teleconferences were held March 10, 2009, September 21, 2009. At the September call DGIEP was informed that P&G pharmaceuticals had been purchased by Warner Chilcott. In October of 2009 Warner Chilcott notified DGIEP that it planned to reformulate.

On a teleconference on March 10, 2009, DGIEP asked P&G to look for opportunities in the Asacol and Asacol HD labels to inform physicians about the health risks associated with exposure to DBP (September 21, 2009 meeting minutes). On September 17, 2009 the Division of Gastroenterology Products (DGP) sent P&G proposed revisions to the Asacol and Asacol HD professional package inserts with important safety information on dibutyl phthalate (DBP) with regard to pregnancy and nursing mothers (Sections 8.1 and 8.3). A new label was approved May 24, 2010, which contained more detailed information regarding the known safety information for DBP. Pregnancy category at that time was changed from Pregnancy Category B to Pregnancy Category C.

The development of a new formulation was challenging and several discussions between Warner Chilcott and DGIEP were held. This resulted in an agreement on the studies required

for approval: a relative bioavailability study and the special dissolution studies. As noted by the CDTL review, “There are special features of these studies: (1) Since oral mesalamine delayed release formulation are considered locally acting, both the BE study and the dissolution testing differ from the standard studies for systemic drugs, and (2) Because Asacol tablets exhibit high intra-subject variability, the reference-scaled average BE methodology is used in lieu of the standard two one-sided t-tests. Note the reviews of many disciplines refer to the proposed capsule formulation as WC3045 capsules.”

Although the currently available human data are limited, DGIEP determined that there is evidence that exposure to DBP from pharmaceuticals presents a potential risk of developmental and reproductive toxicity. This is a concern if Asacol were to be used off label in children, and pregnant or nursing mothers. It was therefore prudent to provide this information in the professional labeling. Because there were other mesalamine products without DBP on the market, and that there was is no substantial human safety information available at that time, it was determined that Asacol with DBP could remain on the market with updated labeling until such time that the applicant could provide a reformulated product for marketing without DBP. The applicant agreed that they would remove Asacol (b) (4) when the new formulation was approved.

The currently approved Asacol 400mg labeling describes the safety concerns as follows:

**Pregnancy:** Pregnancy Category C: There are no adequate and well controlled studies of **Asacol** 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. Animal reproduction studies of mesalamine found no evidence of fetal harm. However, dibutyl phthalate (DBP) is an inactive ingredient in **Asacol's** enteric coating, and in animal studies at doses >190 times the human dose based on body surface area, maternal DBP was associated with external and skeletal malformations and adverse effects on the male reproductive system. **Asacol** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

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 1.6 times (rat) and 3.2 times (rabbit) the recommended human dose, based on body surface area.

Dibutyl phthalate (DBP) is an inactive ingredient in **Asacol's** enteric coating. The human daily intake of DBP from the maximum recommended dose of **Asacol** tablets

is about 21 mg. Published reports in rats show that male rat offspring exposed in utero to DBP ( $\geq 100$  mg/kg/day, approximately 39 times the human dose based on body surface area), display reproductive system aberrations compatible with disruption of androgenic dependent development. The clinical significance of this finding in rats is unknown. At higher dosages ( $\geq 500$  mg/kg/day, approximately 194 times the human dose based on body surface area), additional effects, including cryptorchidism, hypospadias, atrophy or agenesis of sex accessory organs, testicular injury, reduced daily sperm production, permanent retention of nipples, and decreased anogenital distance are noted. Female offspring are unaffected. High doses of DBP, administered to pregnant rats was associated with increased incidences of developmental abnormalities, such as cleft palate ( $\geq 630$  mg/kg/day, about 244 times the human dose, based on body surface area) and skeletal abnormalities ( $\geq 750$  mg/kg/day, about 290 times the human dose based on body surface area) in the offspring.

**Nursing Mothers:** Mesalamine and its N-acetyl metabolite are excreted into 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-5aminosalicylic 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 - 0.017 mg/kg/day of mesalamine and 0.75-2.72 mg/kg/day of N-acetyl-5-aminosalicylic acid. Caution should be exercised when **Asacol** is administered to a nursing woman.

Dibutyl phthalate (DBP), an inactive ingredient in the enteric coating of **Asacol** tablets, and its primary metabolite mono-butyl phthalate (MBP) are excreted into human milk. In pregnant rats, DBP causes fetal reproductive system aberrations/malformations in male offspring [see PRECAUTIONS, Pregnancy]. The clinical significance of this is has not been determined.

### 3. CMC

The formulation of the proposed capsules and the approved Asacol tables are similar except that the proposed capsule formulation uses dibutyl sebacate to replace DBP, in addition, it also has a hydroxypropyl methylcellulose (HPMC) capsule which coats the tablet.

The original review of the NDA identified several issues with the manufacture of the drug substance (especially the “original process” needed to be replaced with an “alternative process”), stability commitment, labeling issues, and site inspection recommendations were pending.

Environmental Assessment: The Applicant’s claim for categorical exclusion is granted by the reviewer.

In the addendum of February 1, 2013 the reviewer noted that all of these issues were resolved, and that the Office of Compliance has made an overall “acceptable” recommendation for the facilities involved. The final recommendation is for approval with an expiration dating period of 18 months.

## ONDQA Biopharmaceutics Review

The reviewer noted that there is no significant risk of alcohol dose dumping with the proposed formulation.

The reviewer recommends the following:

“NDA 204-412 is recommended for approval with a post-marketing commitment as listed below. This is not an approvability issue.”

“The dissolution acceptance criteria you proposed below are accepted on an interim basis.  
0.1N HCl (Type II Paddle 100 RPM, 2 hrs): No individual value exceeds 1% dissolved  
pH 6.0 (Type II Paddle 100 RPM, 1 hr): No individual value exceeds 1% dissolved  
pH 7.2 (Type II Paddle 50 RPM): Q=80% at 1.5 hrs”

“You commit to collect additional dissolution profile data (including the additional 75 min time point) from the stability batches at the scheduled stability time points and from all the batches manufactured during the first year after action date (n=12 for the remaining time points of the ongoing stability protocol; n ≥ 6 for the batch release). These data should be used for setting the final dissolution acceptance criteria.

The reviewer recommended the following postmarket commitment:

Collect additional dissolution profile data (including the additional 75 min time point, n=12) from the stability batches at the scheduled time points and from at least (b) (4) batches manufactured during the first year after action date. These data will be used for the setting of the final dissolution acceptance criteria

*I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months. There are no outstanding issues.*

## **4. Nonclinical Pharmacology/Toxicology**

There were no new nonclinical pharmacology or toxicology studies submitted to this NDA. The removal of DBP from the formulation allowed the reviewers to recommend a change in Pregnancy category back to Pregnancy Category B and removal of the discussion of DBP in the label.

The reviewer summarized information regarding the safety of the excipient dibutyl sebacate. They concluded that there were no safety issues associated with the use of dibutyl sebacate in this formulation.

*I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.*

## 5. Clinical Pharmacology/Biopharmaceutics

Based on communications held with the agency during the drug development, the NDA involves a single dose bioequivalence study PR08210, “A Study to Assess the Relative Bioavailability of Two WC3045 Formulations in Healthy Subjects”, comparing the test (WC3045 capsules) and reference (Asacol 400 mg) formulations in a fully replicate crossover design, and utilizes the reference-scaled BE approach for highly variable drugs. This study was conducted in a fasting state.

During a Type C meeting on November 2, 2010, the details of the pharmacokinetic (PK) and dissolution requirements were discussed further. During this meeting, the Agency agreed with the sponsor regarding the use of partial AUC in addition to the traditional PK parameters (C<sub>max</sub> and AUC) to ensure profile similarity as part of a bioequivalence approach that also includes similarity of dissolution profiles. For partial AUC, Agency recommended characterizing the latter portion of the PK profile. FDA also agreed that a reference scaled BE approach for highly variable drugs would be appropriate.

In advice letters dated February 15, 2011 and December 5, 2011, the agency provided further input on the sponsor’s proposed study protocol. Agency recommended a fully replicate study design (i.e. both test and reference administered twice), and recommended statistical analyses of C<sub>max</sub>, AUC<sub>0-t<sub>l</sub>dc</sub>, AUC<sub>8-48</sub> in the proposed study. The agency noted that they recommend the partial AUC<sub>8-48</sub> hours as opposed to the (b) (4) proposed by the sponsor. This time period (8-48 hours) was perceived by the agency at the time to be more clinically relevant and was expected to be able to detect significant differences in product performance. The Agency also noted that additional exploratory parameters, such as (b) (4) (0-12 and 12-48 hours, etc.) may be included as secondary endpoints.

A pre-submission meeting was held on June 13, 2012 at which time the agency reiterated that a comparative clinical endpoint study will not be required if bioequivalence and dissolution comparability have been established. Agency also clarified that a reference scaled BE approach for highly variable drugs can be employed is applicable even when variability (intra-subject %CV) exceeds 100 %.

The reviewer concluded the following:

“Study PR08210 demonstrates bioequivalence of the test and reference mesalamine formulations under the conditions studied (fasting). The primary endpoints for comparison included C<sub>max</sub>, AUC<sub>0-t<sub>l</sub>dc</sub> as well as a partial AUC parameter AUC<sub>8-48</sub>. The latter partial AUC was recommended by the agency as it was perceived to reflect drug absorption (and therefore drug availability) at the site of action in the colon. Supportive analyses for other partial AUCs also suggested bioequivalence of the two formulations.”

“Due to absence of food-effect information in the NDA for this new delayed release formulation, labeling will need to reflect that dose should be administered under relatively fasted conditions (e.g. 1 h before a meal or 2 h after a meal for this TID administered drug). Label may be revised if food-effect information becomes available. Approved Asacol can be taken with or without food. NDA also includes in vitro release data at various pH conditions,

as well as in vitro alcohol dose-dumping information that is being reviewed by ONDQA Biopharmaceutics Division.”

The Division of Bioequivalence and GLP Compliance (DBGLPC) inspected the pivotal study site. Results from the site inspection resulted in the following recommendations:

- “The data generated from the following samples cannot be assured:
  - o Subject 507345 (b) (6) Period 1, Sample 24 hr
  - o Subject 507355 (b) (6) Period 4, Sample 4 hr
  - o Subject 507355 (b) (6) Period 4, Sample 6 hr
  - o Subject 507376 (b) (6) Period 2, Sample 36 hr
  - o Subject 507393 (b) (6) Period 1, Sample 2 hr
  - o Subject 507396 (b) (6) Period 3, Sample 10 hr”
- “The OCP reviewer should confirm the BE outcomes of study PR-08210 with concentrations using consistently integrated chromatograms in runs #54 and 74.”
- “The other clinical and analytical data from this study are acceptable for your review.”

A re-analysis of the data by clinical pharmacology (see addendum to review, Sandhya Apparaju) as recommended by the inspectors did not result in significant differences, and did not change the finding of bioequivalence.

*I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.*

## 6. Clinical Microbiology

Not applicable; this is an oral formulation.

## 7. Clinical/Statistical-Efficacy

No new clinical efficacy trials were submitted in support of this application. The current application provides results of a relative bioavailability study, comparing the pharmacokinetic profile and bioavailability of WC3045 (Delzicol) to Asacol® 400 mg. Study PR-08210 confirmed that WC3045 capsules have comparable PK profiles and are bioequivalent to Asacol® 400 mg tablets. (Studies are discussed above in Section 5)

## 8. Safety

The safety results of Study PR-08210 were reviewed and no new or unexpected adverse events were seen. The removal of dibutyl phthalate in this new product responds to the safety concern regarding phthalates, especially since potential doses used off label in children result in a high levels exposure to DBP. This recommendation is in keeping with recent FR Notice limiting the use of phthalates in CDER-regulated drugs.

## 9. Advisory Committee Meeting

This application was not taken to an Advisory Committee. This NDA only proposes a formulation change. Outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

## 10. Pediatrics

Pediatric and Maternal Health review of labeling agrees with Pregnancy Category B recommendation and removal of DBP information.

The reviewer notes:

“No pediatric studies were conducted using the proposed formulations. [REDACTED] (b) (4)

[REDACTED]

### Study 2005018:

“This was an open-label, randomized, 29-day parallel-group study to determine mesalamine pharmacokinetics in children and adolescents (N=33) with active UC. [REDACTED] (b) (4)

[REDACTED] Patients were stratified by age (5-8 years and 9-17 years) and randomly assigned to receive every 12 hours one of 3 doses of mesalamine (30 mg/kg/day, 60 mg/kg/day, and 90 mg/kg/day) administered as Asacol® (mesalamine) delayed-release tablets, 400 mg.”

### Study 2007017:

“This was a randomized, double-blind, parallel-group, 6-week study of 2 dose levels (low dose and high dose) of mesalamine administered as Asacol® (mesalamine) delayed-release tablets, 400 mg in pediatric patients aged 5-17 years (N=83) with mildly to moderately active UC.

[REDACTED] (b) (4) Randomization was stratified by weight (17 to <33 kg, 33 to <54 kg, and 54 to 90 kg) and by disease severity (mild and moderate). [REDACTED] (b) (4)

[REDACTED] The pediatric formulation used for this trial was Asacol® 400 mg delayed release tablets.”

### Study 2008085:

“This was a randomized, double-blind, parallel-group, 26-week study of 2 dose levels of Asacol® (mesalamine) delayed-release tablets, 400 mg consisting of a high dose and a low dose in pediatric subjects 5 to 17 years of age for the maintenance of remission of UC. The

(b) (4) This study was terminated early due to challenges with patient enrollment.”

**Pediatric Research Equity Act (PREA):**

The proposed product is a new dosage form. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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

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

PMR: #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.

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

PMR: 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 UC.

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

As noted above the Applicant has conducted three pediatric studies (b) (4)

[Redacted text]

## 11. Other Relevant Regulatory Issues

- DSI Audits, acceptable recommendation
- Financial Disclosure; no issues.

*There are no other unresolved relevant regulatory issues*

## 12. Labeling

- Proprietary name:

The Applicant formally submitted the proposed name Delzicol on January 18, 2013, for further review. Delzicol was, recommended as acceptable by DMEPA and agreed upon by the review team as acceptable.

- Physician labeling (major issues were resolved)
  - Clinical Pharmacology has the following recommendation: “Because the study was conducted under fasting conditions, the labeling will reflect this and recommend that the drug should be administered under relatively fasted conditions (e.g. 1 hour before a meal or 2 hours after a meal). The label may be revised when food-effect information becomes available. Not that the currently approved Asacol tablet can be taken with food.”

DDPDP/OPDP reviewer has the following recommendations:

- “1. Warnings and Precautions in the Highlight section:

Although this section is consistent with the Highlights of Asacol HD (label approved 05/24/10), the Highlights of Lialda (label approved 07/14/11) includes additional risk information in this section. Specifically, Lialda includes the following (in pertinent part): “Mesalamine-induced acute intolerance syndrome has been reported. Observe patients closely for worsening of these symptoms while on treatment.

- Use caution when treating patients who are hypersensitive to sulfasalazine.
- Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported.
- Hepatic failure has been reported in patients with pre-existing liver disease...

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

- “2. Under section 17 PATIENT COUNSELING INFORMATION

OPDP recommends removal of the statement

(b) (4)



The above was conveyed to the Applicant and satisfactorily incorporated into the final labeling.

Dosing frequency for maintenance of remission of UC currently labeled as 1.6g/day in divided doses. The review team located the original NDA review for Asacol tablets and also asked Warner Chilcott to provide further information, as the pivotal study was conducted using a QID dosing schedule. The medical reviewer noted that the pivotal study utilized a QID dosing schedule. However, “a pooled efficacy analysis of four maintenance trials comparing mesalamine to sulfasalazine was relied upon for supportive evidence of the efficacy of Asacol 400 mg tablets. In these studies, Asacol 400 mg tablets was dosed 0.8 g/day to 2.8 g/day in divided doses ranging from twice daily to four times daily. These studies provided evidence that a dosing frequency other than four times daily may be appropriate.”

The reviewer recommended that:

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

- Carton and immediate container labels
  - Review by DMEPA recommended a few changes which were communicated to the Applicant and were addressed to DMEPA’s satisfaction and they recommended approval
- Medication Guide: a Medication Guide was not required.

### **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action – approval of (WC3045) Delzicol (mesalamine) 400 mg delayed release capsules for currently approved Asacol (mesalamine) 400 mg tablet indications.

- Risk Benefit Assessment

For this new formulation the risks due to exposure to DBP are eliminated, therefore the risk benefit has improved with this new formulation which is DBP free.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS): None needed.
- Recommendation for other Postmarketing Requirements and Commitments

The PREA Postmarket Required Studies are listed above (Section 10).

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There is one CMC Postmarket Commitment regarding improvements in dissolution specifications as recommended by the review team as follows:

PMC: 2011-3

Collect additional dissolution profile data (including the additional 75 min timepoint, n=12) from the stability batches at the scheduled time points and from at least <sup>(b)</sup><sub>(4)</sub> batches manufactured during the first year after action date. These data will be used for the setting of the final dissolution acceptance criteria

Warner Chilcott agreed to the following timeline for completion:

Final Protocol Submission: NA  
Study/Trial Completion: 02/2014  
Final Report Submission: 05/2014

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

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JOYCE A KORVICK  
02/01/2013