

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204412Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 204412
Product Name: Delzicol (mesalamine) Delayed-Release Capsules

PMR/PMC Description: A randomized, double-blind study in pediatric patients ages 5 to 17
2011-1 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

PMR/PMC Schedule Milestones: Final Protocol Submission: 08/31/2013
 Study/Trial Completion: 05/31/2015
 Final Report Submission: 09/30/2015
 Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study/clinical trial is to provide safety and efficacy data for WC3045 capsules to inform the use of this drug in pediatric patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

The proposed acceptance criteria for the dissolution testing are as follows:

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

However, the data available support a criterion of Q=80% at 75 minutes at pH 7.2 and therefore this criterion was recommended by the Reviewer.

After the recommendation was conveyed to the Applicant, they proposed a post marketing commitment to collect additional data in order to set an appropriate dissolution acceptance criterion at pH 7.2. Considering the limitation of the available data, FDA accepted their post-marketing proposal with a modification on the time frame.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Collection of additional dissolution profile data (including an additional timepoint at 75 minutes, 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 of the drug product.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Additional in vitro dissolution data

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

ANISSA A DAVIS
01/31/2013

STACY R BARLEY
01/31/2013

ANIL K RAJPAL
01/31/2013

SUE CHIH H LEE
01/31/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	TRADENAME (mesalamine) delayed-release capsules, for oral use
Applicant	Warner Chilcott Company, LLC
Application/Supplement Number	NDA 204412
Type of Application	Original Submission
Indication(s)	For the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis
Established Pharmacologic Class ¹	None listed in HL
Office/Division	ODE III/DGIEP
Division Project Manager	Anissa Davis
Date FDA Received Application	August 1, 2012
Goal Date	February 1, 2013
Date PI Received by SEALD	January 23, 2013
SEALD Review Date	January 24, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: .

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: **“These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”**

Comment: *In both places, name of drug product is identified as "TRADENAME." DMEPA to notify DGIEP if proposed proprietary name (DELZICOL) is acceptable. If/when the proprietary name is "accepted," DGIEP will inform applicant to insert proprietary name throughout the PI where "TRADENAME" is used as a placeholder. Also, the HL limitation statement must be on the line immediately beneath the HL heading. There is a space between the two. Delete the extra space.*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment: *Product title is bolded but must insert proprietary name (when determined "acceptable" by DMEPA) where "TRADENAME" is used as a placeholder.*

Initial U.S. Approval

NO

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

Comment: *Initial U.S. approval is not placed immediately beneath the product title. There is a space between the two. Delete the extra space.*

Boxed Warning

N/A

12. All text must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *The established pharmacologic class(Aminosalicylate) is not listed in HL; must include.*

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Selected Requirements of Prescribing Information

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- N/A** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *If you approve this application in January, the revision date must read: Revised: 01/2013, and not "0X/2013." However, if you approve on the PDUFA date (2/1/13), then it must read: Revised: 02/2013.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Selected Requirements of Prescribing Information

Comment: For DRUG INTERACTIONS section, subsection headings 7.1 and 7.2 are missing from the TOC. Insert.

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: Cross reference in CONTRAINDICATIONS section should read: [see Warnings and Precautions (5.3), Adverse Reactions (6.2), and Description (11)], not [see Warnings and Precautions(5.3), Description(11), Adverse Reactions(6.2)].

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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 clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JEANNE M DELASKO
01/24/2013

LAURIE B BURKE
01/24/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

M E M O R A N D U M

Date: Jan 23, 2013

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

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

Lynne Yao, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

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

Drug: WC3045 (mesalamine) Delayed-Release Capsule, 400mg
Proposed name: (b) (4)

Re: Input on question regarding PREA requirement

Sponsor: Warner Chilcott Pharmaceuticals, Inc.

Proposed Indication: Treatment of moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis in adults.

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

Proposed Dosing regimen: Adults only
For the treatment of mildly to moderately active ulcerative colitis: The usual dosage in adults is two 400-mg tablets to be taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks.

For the maintenance of remission of ulcerative colitis:

The recommended dosage in adults is 1.6 grams daily in divided doses. Treatment duration in the prospective, well-controlled trial was 6 months.

Application Number: NDA 204-412

Consult Request:

“Questions for PMHS:

1. Does PMHS agree that (b) (4) is adequate to fulfill the PREA requirement for NDA 204-412 (phthalate free mesalamine formulation)?
2. Is the new size (b) (4) capsule (with (b) (4)) an age appropriate pediatric formulation? If not, does PMHS have any recommendations on the most appropriate pediatric formulation for this product (e.g., granules)?”

Materials Reviewed:

- Meeting Request (April 24, 2012)
- Current Asacol Labeling (April 23, 2009)
- Asacol HD 800 mg tablet, NDA 21-830, Approval letter (May 29, 2008)
- Guidance for Industry: Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products (Draft, March 2012)¹
- PeRC PREA Subcommittee Meeting Minutes (April 9, 2008)
- Written Request for Asacol (mesalamine), NDA 19-651 (June 30, 2008)
- PMHS consult review on Asacol 400 mg tablets, IND 26,093 (July 16, 2012)

Background:

WC3045 is a phthalate-free formulation of mesalamine, intended for use in ulcerative colitis. Asacol (NDA 19-651) is a locally acting aminosalicylate formulated for delayed release oral administration approved in January 1992 for the treatment of moderately active ulcerative colitis (UC) and for the maintenance of remission of UC in adults. In May, 2008, Asacol HD, an 800 mg delayed-release tablet (NDA 21-830) was approved for the treatment of moderately active UC in adults. The sponsor was contacted in March, 2009 to discuss potential adverse reproductive and fetal developmental effects with dibutyl phthalate (DBP), an excipient in Asacol products. Thus, prompted by encouragement from FDA, the sponsor developed this new phthalate-free formulation of Asacol (WC3045 capsule) in which dibutyl phthalate has been replaced with an alternate plasticizer, dibutyl sebacate. The sponsor submitted an NDA for WC3045 delayed-release 400 mg capsules on August 1, 2012. According to the sponsor, the NDA includes a bioavailability study that demonstrates that the WC3045 (phthalate-free) capsules and the currently marketed Asacol 400 mg tablets are bioequivalent. Therefore, the sponsor claims the efficacy of WC3045 is equivalent to Asacol 400 mg tablets, the approved

¹ Guidance for Industry: Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products (Draft, March 2012)

reference product, as well. The sponsor plans to replace the currently marketed Asacol 400 mg tablets with the new phthalate-free formulation (WC3045 capsules) and following the anticipated approval of WC3045 capsules, the sponsor plans to discontinue marketing the Asacol 400 mg tablets. Of note, the sponsor also plans (b) (4)



Reviewer comment: In August, 2009, the FDA stated that as an alternative to full clinical efficacy studies, a combination of dissolution and PK studies may be submitted to evaluate the comparability of the reformulated Asacol and Asacol HD tablets to the currently marketed products.² However, the sponsor had not developed the phthalate-free reformulation at the time of this agreement. The developed phthalate-free reformulation, the WC3045 capsule, is larger than the currently marketed Asacol 400 mg tablet. Therefore, the implications of the larger size and dosage form of the WC3045 capsule were not appreciated until recently.

 (b) (4)

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff (PMHS) to provide input on the sponsor's pediatric development plan, provide assistance with preparation for meeting with the Pediatric Review Committee, participate in labeling, and preparation for an industry meeting on January 15, 2013. DGIEP has specifically requested PMHS feedback on whether the

 (b) (4)

² Memorandum of Meeting Minutes for Asacol HD, NDA 21-830 and Asacol, NDA 19-651 (August 24, 2009)

(b) (4)

A Type C meeting to discuss the development of an age appropriate formulation (IND 26093) is tentatively scheduled for January 15, 2012 and DGIEP has requested PMHS' attendance and participation

Regulatory Background:

Because Asacol, 400 mg tablet, (NDA 19-651) was approved in January, 1992, prior to the passage of Pediatric Research Equity Act (PREA), PREA does not apply to the innovator Asacol 400 mg product. However, a

(b) (4)

When Asacol HD (NDA 21-830, 800 mg tablet) was approved on May 29, 2008, PREA was triggered. Pediatric studies were waived for ages birth to 4 years because studies were deemed to be impossible or highly impractical due to the small number of pediatric ulcerative colitis patients less than 5 years of age. One deferred study under PREA was required for pediatric patients age 5 to 17 years as follows:

Conduct a study in pediatric patients ages 5 to 17 years with ulcerative colitis using an age-appropriate formulation (i.e., an oral mesalamine formulation appropriate for pediatric dosing), such as your approved product, Asacol®. The study will evaluate the pharmacokinetics, safety, and clinical response of pediatric patients undergoing six weeks of oral mesalamine therapy. The study will be a randomized, double-blind study comparing at least two different dose levels of mesalamine and it will enroll at least 40 pediatric patients in each dosing arm.³

At the time the PREA PMR for Asacol HD 800 mg tablets was established,

(b) (4)

³ Asacol HD, NDA 21-830 Approval letter (May 29, 2008)

(b) (4)

Comments on PREA and the Partial Waiver Request for Asacol (WC3045):

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. Although, dibutyl phthalate and dibutyl sebacate are inactive ingredients, and a substitution of these plasticizers to create the new phthalate-free mesalamine formulation would not trigger PREA, the change from a tablet to a capsule formulation constitutes a new dosage form, thereby prompting the requirement for pediatric studies.

A waiver may be granted for one of the following reasons:

- A. Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).
- B. The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
- C. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of pediatric patients in the pediatric age group(s) for which a waiver is being requested.
- D. The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed. Note: Sponsor must provide data to support this claim for review by the Division, and this report submitted by the Sponsor will be publicly posted.

The sponsor requests a partial waiver of pediatric studies in children 0 to 4 years of age due to the small number of pediatric ulcerative colitis patients less than 5 years of age making the conduct of studies in this age group impossible or highly impractical. The sponsor also requests a deferral of studies in pediatric patients age 5 to 17 years of age,

(b) (4)

The sponsor acknowledges, however, the larger size of the WC3045 capsule (size (b) (4) mm) compared to the Asacol 400 mg tablet (b) (4) mm) may pose a difficulty for pediatric patients to swallow and plans to address the requirement of an age appropriate formulation as part of the deferral for this NDA (204-412).

Reviewer comment: The sponsor has submitted justification supporting this partial waiver request based on epidemiologic and use data, and PMHS defers to DGIEP to determine if the provided information is accurate and sufficient. Criterion B and C do not apply. The proposed partial waiver appears reasonable on a scientific basis and is consistent with recent practice for other UC drugs such as Lialda (mesalamine) delayed release tablet and Apriso (mesalamine) extended release capsule. However, the sponsor needs to demonstrate that the new WC3045 capsule is an acceptable formulation for the age range studied, or make reasonable attempts to produce one. If the sponsor is unable to produce an age-appropriate formulation, data must be provided to support this claim for review by the Division, and the submitted report will be publicly posted.

Pediatric Assessment:

The sponsor plans to

(b) (4)

[Redacted text block]

[Redacted text block]

However, DGIEP must also determine that the submitted special dissolution study and PK assessments of WC3045 establish bioequivalence between the new WC3045 400 mg capsule and the existing Asacol 400 mg tablet. Furthermore, due to potential swallowing difficulties because of its size, the WC3045 capsule would not be considered to be an age appropriate formulation for the youngest patients in the proposed relevant pediatric age group of 5 to 17 year-olds. Therefore, studies of the proposed (b) (4) age appropriate formulation would also be necessary to provide a complete pediatric assessment for WC3045 (see below). Additionally, a palatability/swallowability study to determine pediatric patient's ability to ingest both the WC3045 capsule and the proposed (b) (4) age appropriate formulation may need to be conducted.

To fulfill the pediatric assessment for the maintenance indication, the sponsor proposes to

(b) (4)

Discussion of the Age-Appropriate Formulation:

The sponsor has completed a bioavailability study including a special dissolution study and PK assessments on the WC3045 capsules. However, since the WC3045 capsules are size (b) (4) and may be difficult for younger pediatric patients to swallow, the sponsor proposes

(b) (4) to provide an age appropriate formulation. Per the sponsor, this new formulation

(b) (4). In order for the propose (b) (4) to be an acceptable option to satisfy the requirement for an age appropriate formulation, the delayed release properties of the product will need to be maintained when th (b) (4)

Therefore, DGIEP has recommended that content uniformity testing of (b) (4) should be performed. Input from CMC and clinical pharmacology staff should be considered to evaluate these issues. Given the difference in (b) (4) formulation from the WC3045 capsule, a bioavailability study alone may not be sufficient to show equivalence of the new (b) (4) formulation to either the current WC3045 capsule or the currently marketed Asacol 400 mg tablet. Therefore, efficacy may not be able to be extrapolated and a clinical trial evaluating both the proposed (b) (4) may be required. The sponsor will need to provide justification that the proposed (b) (4) formulation can be bridged with the WC3045 capsule of Asacol 400 mg tablets.

Reviewer comment: (b) (4)

Comments on the Pediatric Study Plan:

(b) (4)

The PREA PMR for WC3045 should include studies similar to (b) (4) the Asacol HD PREA PMR. (b) (4)

However, as stated above, pediatric study requirements will also need to incorporate development of an age appropriate formulation and address the proposed maintenance indication. Thus, PMHS recommends that the PREA requirements be defined broadly in case review of (b) (4)

Comments conveyed to the Division in preparation for the PeRC meeting:

(1) In order for (b) (4) the pediatric assessment must also be reviewed by the Pediatric Review Committee (PeRC).

(2) The new WC3045 capsule is size (b) (4) which is larger than the marketed Asacol 400 mg tablets and may be difficult for pediatric patients to swallow. PREA requires you to make reasonable attempts to produce an age appropriate pediatric formulation. If you are unable to develop an age-appropriate formulation, you must provide data to support this claim for review by the Agency, and the submitted report will be publicly posted. The proposed (b) (4)

(3) A partial waiver for the 0 to 4 year age group appears appropriate. However, the Agency must be satisfied that the submitted scientific rationale to support your partial waiver request which includes epidemiologic information and use data for Asacol and other mesalamine products in pediatric patients is accurate and sufficient.

PMHS and DGIEP, with concurrence by PeRC, agreed to the following PREA PMR:

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

Protocol Submission Date: 8/31/2013

Study Completion Date: 5/31/2015

Final Report Submission: 9/30/2015

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

Protocol Submission Date: 8/31/2013

Study Completion Date: 5/31/2016

Final Report Submission: 9/30/2016

PMHS Review of labeling:

Proposed labeling dated August 1, 2012:

8.4 Pediatric Use

Safety and effectiveness of mesalamine delayed-release in pediatric patients have not been established.

The current proposed language for the Pediatric Use subsection is appropriate except that the product name, which has not been determined, should replace the language “mesalamine delayed-release”.

Recommended labeling:

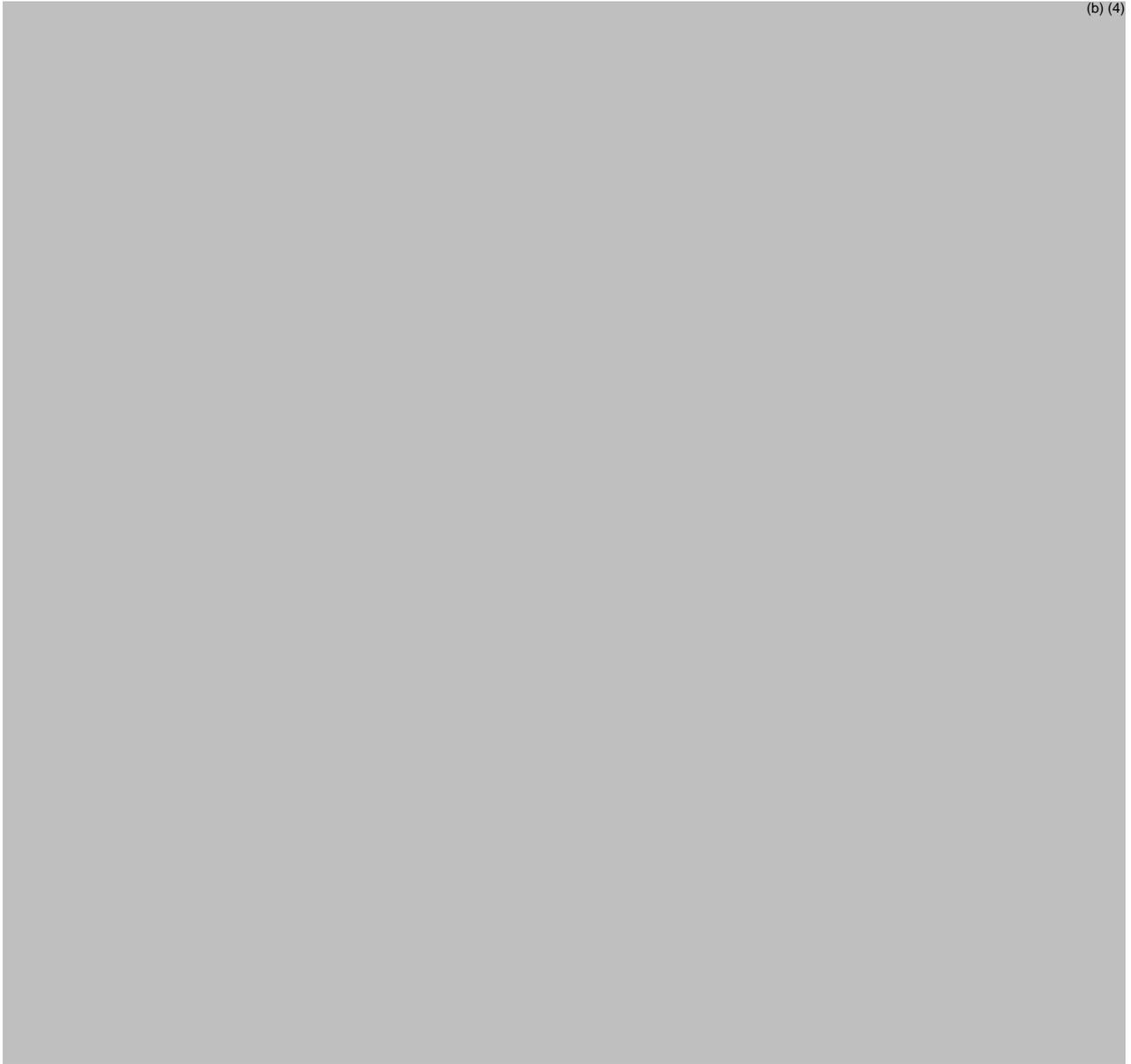
8.4 Pediatric Use

Safety and effectiveness of TRADENAME in pediatric patients have not been established.

PMHS participated in the internal PeRC preparation meetings on December 3, 2012, December 11, 2012, and January 7, 2013, and also assisted DGIEP with the PeRC paperwork for discussion at PeRC on January 9, 2013. PMHS participated in the team and labeling meetings held between November 2012 and January 2013. PMHS also participated in the pre-sponsor meeting for IND 26093 on January 8, 2013 and the sponsor meeting on January 15, 2013. Our input is reflected in the meeting minutes and comments conveyed to the Sponsor.

Appendix 1:

(b) (4) 5



(b) (4)

5

(b) (4)

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/s/

ERICA D RADDEN
01/25/2013

HARI C SACHS
01/25/2013
I agree with these recommendations.

LYNNE P YAO
01/30/2013

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

*****Pre-decisional Agency Information*****

Memorandum

Date: January 16, 2013

To: Anissa Davis, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Stacy Barley, Senior Regulatory Project Manager
DGIEP

From: Kathleen Klemm, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204412 - OPDP labeling comments for TRADENAME (mesalamine)
delayed-release capsules, for oral use

OPDP has reviewed the proposed Prescribing Information (PI), for TRADENAME (mesalamine) delayed-release capsules, for oral use, submitted for consult on August 28, 2012, and offers the following comments.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled, "NDA 204412 SCPI for OPDP review 1.11.13 Clinical version.doc" sent via email from Anissa Davis on January 11, 2013.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions, please contact Katie Klemm at 301-796-3946 or Kathleen.Klemm@fda.hhs.gov.

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

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/s/

KATHLEEN KLEMM
01/16/2013

INTRODUCTION

On August 1, 2012, Warner Chilcott Company, LLC submitted a New Drug Application submission for Mesalamine Delayed-Release Capsules, 400 mg, NDA 204412, to provide for a new dosage form of mesalamine indicated for the treatment of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC. The proposed dosing regimen is same as for the Applicant's Asacol (mesalamine) delayed-release tablets, 400 mg, NDA 19651. This mesalamine product provides for a new mesalamine formulation in which dibutyl phthalate (DBP) that is present in the tablet enteric coating is replaced with the [plasticizer dibutyl sebacate (DBS) and the tablet is encapsulated.

On November 30, 2012, the Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and comment on the proposed pregnancy category change from C to B and to review and comment on the proposed pregnancy and nursing mothers subsections of mesalamine delayed-release capsule labeling.

BACKGROUND

Mesalamine is a locally acting aminosalicylate indicated for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis. Approximately 28 percent of the mesalamine in mesalamine delayed-release formulations is absorbed after oral ingestion. Mesalamine products were originally approved with dibutyl phthalate in the enteric coating of the products and recent publications described human and reproductive concerns with exposure to dibutyl phthalate.

In 2009, DGIEP requested that Applicants with mesalamine products submit development plans for the removal of dibutyl phthalate from their products and to update pregnancy labeling with a pregnancy category change from pregnancy category B to pregnancy category C along with information on human reproductions and development concerns with the use of dibutyl phthalate. Mesalamine was originally classified as a pregnancy category B product because no adverse effects were observed in animal reproduction studies. On December 5, 2012, FDA issued Guidance for Industry: Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products.¹ Several mesalamine-containing products manufactured by other companies have already been re-formulated to remove the dibutyl phthalate and have had their pregnancy category re-classified as pregnancy category B.

On March 11, 2009, PMHS-MHT was consulted by DGIEP on appropriate pregnancy and nursing mothers labeling revisions regarding the presence of phthalates in mesalamine products (see Maternal Health Review, July 23, 2009). Mesalamine pregnancy and nursing mothers labeling was updated at that time to include the human reproduction and developmental concerns with pregnancy exposure to dibutyl phthalate, as well as updated with available published human pregnancy and lactation data associated with the use of mesalamine.

¹ www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm330792.htm - 18k - 2012-12-05

APPLICANT PROPOSED PREGNANCY AND NURSING MOTHERS LABELING

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate well controlled studies of mesalamine delayed-release 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.

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 $\frac{(b)}{(4)}$ times (rat) and $\frac{(b)}{(4)}$ times (rabbit) the recommended human dose, based on body surface area.

8.3 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-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. Caution should be exercised when mesalamine delayed-release is administered to a nursing mother.

DISCUSSION AND CONCLUSIONS

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When

only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount.

This mesalamine product is appropriately labeled for use in pregnant and lactating women. A pregnancy category B is the appropriate pregnancy category classification for this product because animal data as well as limited human data failed to show evidence of fetal harm. The dibutyl phthalate information has been removed from labeling as the product as been re-formulated without this plasticizer in its enteric coating.

RECOMMENDATIONS

PMHS-MHT recommends the following re-structuring of the pregnancy and nursing mothers labeling for this mesalamine product, with the addition of subheadings under the pregnancy subsection of labeling. PMHS-MHT updated the language in the pregnancy and nursing mothers subsections of mesalamine product labeling in 2009.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Pregnancy Category B: There are no adequate and well controlled studies of mesalamine delayed-release 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.

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

8.3 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-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. Caution should be exercised when mesalamine delayed-release is administered to a nursing woman.

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/s/

JEANINE A BEST
01/09/2013

MELISSA S TASSINARI
01/09/2013

LYNNE P YAO
01/11/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: January 9, 2013

Reviewer: Denise V. Baugh, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: (b) (4) (Mesalamine) Delayed Release Capsule
400 mg

Application Type/Number: NDA 204412

Applicant/sponsor: Warner Chilcott

OSE RCM #: 2012-1832

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for (b) (4) (Mesalamine) Delayed-release Capsules for NDA 204412 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

(b) (4) is a revised formulation of Asacol (Mesalamine) Delayed Release Tablets (NDA 019651). Asacol was first approved in January, 1992. Asacol contains the excipient, dibutyl phthalate (DBP) which is associated with reproductive system aberrations compatible with disruption of androgenic dependent development in rats. Additionally, DBP and its primary metabolite are also excreted into human milk. As a result of these findings, the Asacol prescribing information was updated. Also, FDA requested that the Applicant revise the formulation to remove DBP.

As a result, the Applicant submitted a new NDA for (b) (4) (Mesalamine) Delayed-release Capsules. The NDA Application has been approved for a priority review due to the safety issues associated with the inactive ingredient, DBP. The proprietary name, (b) (4) is being evaluated in a separate review (OSE Review # 2012-2373).

1.2 PRODUCT INFORMATION

The following product information is provided in the August 7, 2012 proprietary name submission.

- Active Ingredient: Mesalamine
- Indication of Use: Treatment of mildly to moderately active ulcerative colitis and maintenance of remission of ulcerative colitis
- Route of Administration: Oral
- Dosage Form: Delayed-release Capsules
- Strength: 400 mg
- Dose and Frequency: 800 mg by mouth three times daily or 1600 mg by mouth daily in divided doses
- How Supplied: Bottles of 180 capsules
- Storage: Room temperature
- Container and Closure System: Child-resistant cap

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Asacol (Mesalamine) medication error reports. We also reviewed the (b) (4) labels and package insert labeling submitted by the Applicant. However, the proposed name, (b) (4) was withdrawn after a teleconference with the Applicant and the proposed name,

(b) (4) was submitted. Therefore, our review considered this recent submission in our assessment of the label and labeling (although updated label/labeling was not available).

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) using the strategy listed in Table 1.

Date	October, 2012
Drug Names	Asacol (trade name) Asaco% (verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 68 cases. Each case was reviewed for relevancy and duplication. After individual review, 54 cases were not included in the final analysis for the following reasons:

- Tablets in stool/residue, which may be expected from this product and is stated in the labeling
- Not enough information in the case to identify if an error occurred
- Adverse event unrelated to medication error
- Product complaints
- Intentional overdose or death unrelated to Asacol

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on November 8, 2012 for additional cases and actions concerning Asacol. No additional cases were identified.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 7, 2012 (Appendix A)
- Carton Labeling submitted August 7, 2012 (Appendix B)
- Insert Labeling submitted August 7, 2012 (no image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Asacol labels and labeling (OSE review # 2009-1219) and Asacol HD proprietary name and labels and labeling (OSE reviews # 2008-1859, and # 2012-1219) and we looked at the reviews to ensure all our recommendation were implemented or considered for this review.

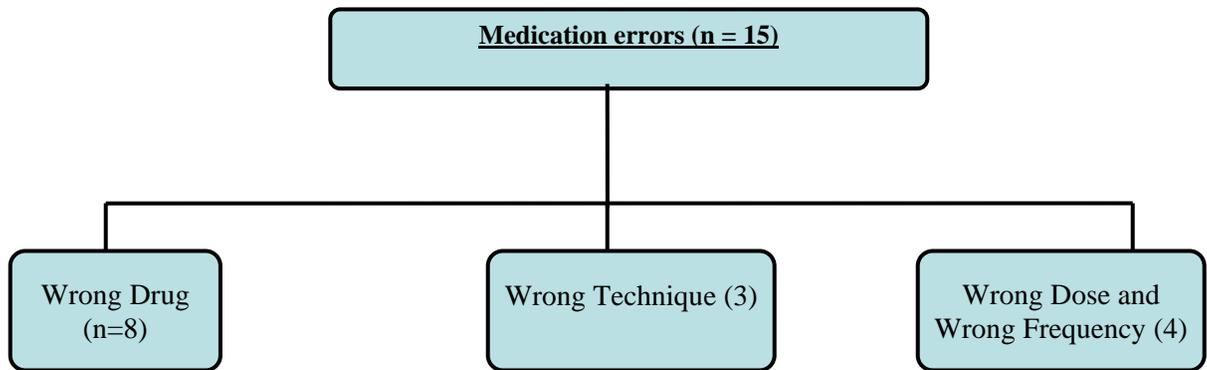
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the (b) (4) product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, fourteen Asacol medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Of note, one case involved more than one type of error (e.g., wrong dose and wrong frequency), therefore the number of error (15) is greater than the number of cases (14). Figure 1 provides a stratification of the number of errors included in the review by type of error. Table 2 provides listings of all case numbers for the cases summarized in this review.

Figure 1: Asacol medication errors (n =15) categorized by type of error



3.1.1 Wrong Drug (n = 8)

There were eight wrong drug errors and four of them involved confusion between Oscal and Asacol. Three of the four cases suggested that the error was a result of illegible handwriting (n = 2) or a nurse's misinterpretation of a verbal order from the physician

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>. Accessed June 1, 2011.

(n = 1) and the remaining case did not provide sufficient detail to determine the cause of the error. No outcomes were stated in any of the four cases.

The remaining four cases were isolated errors each involving confusion between Asacol and either Actos, Visicol, Ansaid, or Avelox. One of the cases cited a process-related problem in which the pharmacy refilled a prescription for Actos with Asacol tablets during a busy period when there was a staff shortage. The reason for the confusion was not given in the remaining three cases. One patient experienced worsening ulcerative colitis when Avelox was dispensed instead of Asacol. No outcomes were given in the other three cases.

3.1.2 Wrong Technique (n =3)

Three wrong technique cases reported cutting Asacol tablets into 4 pieces, cutting it in half, and chewing the tablets respectively. A physician prescribed a dose less than 400 mg in one of these cases and one of the patients manipulated the tablet to facilitate swallowing. One case reported an outcome of cardiomyopathy. However, in this case the reporting physician and cardiologist disagreed regarding Asacol's role in this adverse event.

3.1.3 Wrong Dose or Wrong Frequency (n =4)

These cases described instances where the patients took their entire daily dose at one time of day (wrong dose and frequency) or where a patient separated their 'twice daily' regimen by 6 hours rather than 12 hours. (We note the insert labeling does not clearly state a recommended interval for administration of this product.) One of the three reporters (a nurse) stated that this regimen was prescribed by their physician. Reported outcomes included severe lower abdominal pain, bloody diarrhea, a 5 pound weight loss and a seizure (which is an unlabeled adverse event). The seizure was believed to be caused by taking the doses too close together.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The majority of the medication errors were wrong drug errors and four of them involved the names Oscal and Asacol. The reporters cited illegible handwriting and misinterpretation of a verbal order as contributing factors and we note that the names Oscal and Asacol have strong orthographic and phonetic similarity which may have caused confusion. However, the Applicant proposes to market the revised formulation under a different proprietary name which will be reviewed separately (OSE Review # 2012-2373).

We also identified cases of wrong dose and wrong frequency where the patients took their entire dose at one time of day or at a frequency which was not recommended. We note that the recommended dose and administration section of the insert labeling is stated to be "1.6 grams daily, in divided doses" for maintenance of remission of ulcerative colitis. This language may be interpreted to mean that any dosing regimen is acceptable such as "800 mg twice daily" or "400 mg four times daily". Stating a specific dosing regimen will help to clarify how to take this product and potentially minimize side effects, and optimize efficacy. This will also be consistent with the administration

directions given for the treatment regimen. We communicated our concerns to the Division and have repeated this recommendation in Section 5.

We retrieved three cases of wrong technique (e.g., chewing and cutting) despite the statements present in the insert labeling and on the side panel of the container label to “swallow whole without cutting, breaking, or chewing”. This information also exists in the Patient Counseling Information Section of the labeling (Section 17). However, relocating this statement from the side panel to the principal display panel of the container (for the commercial and sample product) may help to improve its prominence.

Additionally, we assessed whether the provision of a sample packaging configuration with 12 tablets is reasonable based upon the recommended dosing and administration for this drug product. We find that the provision of this configuration is reasonable as it provides product for 2 days of treatment for the patient.

Finally, the Agency has not yet received a food study from the Applicant for this revised formulation which would address the impact of food on the administration of this product. The previous formulation (‘Asacol’) could be ingested with or without food, but the effect of food on this new formulation is unknown. Therefore, the division has decided that the product should be taken on an empty stomach pending the Applicant’s submission of this information. Specifically, this product should be given ½ hour before or 2 hours after a meal and this statement was included in the dosage and administration section of the insert labeling. It should also be repeated on the container label and carton labeling.

4 CONCLUSIONS

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 safe use of the product. See our recommendations below.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Division

Consider revising the dosage and administration section for the remission of ulcerative colitis to provide more specific guidance concerning the dose and frequency of administration. Specifically, the phrase “1.6 grams daily, in divided doses” allows for any number of dose and dosing frequency directions (e.g., 800 mg twice daily or 400 mg four times daily), but does not provide guidance for a preferred dosing regimen.

B. Comments to the Applicant

1. All Label and Labeling (container label [180 count] sample container label [12 count], and sample carton labeling [12 count])
 - a. Update all labels and labeling to remove reference to the proprietary name, (b) (4) as this name has been denied.

- b. Although it appears the established name is printed in letters that are at least half as large as the letters comprising the proprietary name, the prominence of the established name is lessened due to the small font thickness in relation to the proprietary name. Revise the presentation of the established name taking into account all pertinent factors, including font thickness, typography, layout, contrast and other printing features in accordance with 21 CFR 201.10(g)(2).
 - c. Remove the statement “per capsule” as the dosage form (‘capsule’) is already stated and therefore this statement is redundant.
 - d. Locate the strength statement (‘400 mg’) to appear just below the dosage form (‘delayed-release capsules’).
 - e. The lines incorporated into the graphic are too prominent and interfere with the readability of other information such as the net quantity statement. Please revise or delete the lines.
 - f. Revise the presentation of the “Rx Only” statement, the net quantity statement (“12 capsules”) and the statement “Sample-Not for Sale” appearing at the lower part of the principal display panel to improve its readability. The use of overly fanciful font makes such statements difficult to read.
 - g. Add this important dosing message on to the label: “Take each dose at least at least ½ hour before or 2 hours after a meal”.
 - h. Incorporate space between all statements on the principal display panel to assist with readability.
- 2. Sample Tray
See Recommendations A(1)(a) and A(1)(b).
 - 3. Container Label (180 count) and Sample Carton Labeling (12 count)
Ensure that the “New formulation” alert is implemented only for the first six months of new product marketing.
 - 4. Sample Carton Labeling
Revise the presentation of the “Rx Only” statement, the net quantity statement (“12 capsules”) and the statement “Sample-Not for Sale” appearing at the lower part of the principal display panel to improve its readability. The use of the yellow outline with white lettering makes these statements difficult to read on the images provided to the Agency.
 - 5. Sample Container Label
Consider moving the lot and expiration date to the side panel for the sample container label to accommodate the above recommendations

If you have further questions or need clarifications, please contact Phong (Pete) Do, OSE Project Manager, at 301-796-4795.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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/s/

DENISE V BAUGH
01/09/2013

LUBNA A MERCHANT
01/09/2013

SCOTT M DALLAS
01/09/2013

MEMORANDUM

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

DATE: January 8, 2013

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III

Edward D. Bashaw, Ph.D.
Director
Division of Clinical Pharmacology III
Office of Clinical Pharmacology

FROM: Sripal R. Mada, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 204-412 Mesalamine Delayed
Release Capsules, 400 mg from Warnex Chilcott Company,
LLC, USA

At the request of the Division of Gastroenterology and Inborn Errors Products (DGIEP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected the following study:

PR-08210: "A Study to Assess the Relative Bioavailability of Two WC3045 Formulations in Healthy Subjects, Study PR-08210"

Clinical:

The inspections of two clinical portions were conducted by Ethan P. Stegman (ORA) at **Comprehensive Clinical Development, Fort Myers, FL** and **Comprehensive Clinical Development, Miramar, FL**. Following the inspections (October 6-9, 2012 and October 22-26, 2012, respectively), no Form FDA-483 was issued.

The inspection of a third clinical portion was conducted by Todd R. Lorenz (ORA) at **Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX (WCTEPS)**. Following the inspection (October 22-29, 2012), Form FDA-483 was issued (**Attachment 1**). The firm's response was received on November 13, 2012 (**Attachment 2**).

The Form FDA-483 observation, WCTEPS response to Form FDA-483 and our evaluation follow:

1. **Failure to ensure that an investigation was conducted in accordance with the protocol for study #PR-08210. Specifically, protocol section 12.1, "PK blood sampling and processing," said that "the time between sample collection and placement in the freezer is not to exceed 60 min." However, the following deviations were observed in the clinical investigator files:**
 - Subject 507319 (b) (6), Period 3, Sample at 30 hr was withdrawn at 12:18 but plasma was not frozen until 15:13, a period of 175 min after withdrawal.
 - Subject 507344/(b) (6), Period 1, Sample 12 hr was withdrawn at 18:43 but plasma was not harvested or shipped to the analytical lab for analysis.
 - Subject 507345 (b) (6), Period 1, Sample 24 hr was withdrawn at 06:44 but without documentation of when plasma was frozen.
 - Subject 507355/(b) (6), Period 4, Sample 4 hr was withdrawn at 10:54 but without documentation of when plasma was frozen.
 - Subject 507355/(b) (6), Period 4, Sample 6 hr was withdrawn at 12:54 but without documentation of when plasma was frozen.
 - Subject 507376/(b) (6), Period 2, Sample 36 hr was withdrawn at 19:15 but without documentation of when plasma was frozen.

- Subject 507393/(b)(6), Period 1, Sample 2 hr was withdrawn at 09:32 but without documentation of when plasma was frozen.
- Subject 507396/(b)(6), Period 3, Sample 10 hr was withdrawn at 17:35 but without documentation of when plasma was frozen.

WCTEPS responded that these deviations in PK sampling were documented in source records as a protocol deviation log. In addition, WCTEPS remarked that the concentration-time profiles displayed in the final report for these subjects did not show anomalies at the times in question for these samples.

In the opinion of the reviewer, the data from subject 507319/(b)(6)/Period 3, sample 30 hr can be accepted because (b)(4) (analytical site) confirmed 5-ASA bench-top stability for about 6.5 hours (390 min).

The data from the following samples are not assured and their accuracy cannot be confirmed, as WCTEPS did not record when the plasma samples were frozen.

- Subject 507345/(b)(6), Period 1, Sample 24 hr
- Subject 507355/(b)(6), Period 4, Sample 4 hr
- Subject 507355/(b)(6), Period 4, Sample 6 hr
- Subject 507376/(b)(6), Period 2, Sample 36 hr
- Subject 507393/(b)(6), Period 1, Sample 2 hr
- Subject 507396/(b)(6), Period 3, Sample 10 hr

Analytical:

The inspection of the analytical portion was conducted by (b)(4) at (b)(4)

Following the inspection (December 3-7, 2012), Form FDA-483 was issued (**Attachment 3**). The firm's response was received on December 21, 2012 (**Attachment 4**).

The Form FDA-483 observation, (b)(4) response to Form FDA-483 and our evaluation follow:

1. **Failure to conduct an experiment to evaluate the effects of hemolysis on 5-Amino Salicylic acid (5-ASA) quantification. In addition, failure to document the number of hemolysed samples after**

receiving plasma samples from the three clinical sites.

In their response to Form FDA-483, (b) (4) acknowledged this observation and performed additional hemolysis testing for 5-ASA by evaluating low and high QC samples with 1%, 2% and 5% hemolysis. The hemolysed QC samples were analyzed against calibrators and QCs prepared in non-hemolysed human plasma. (b) (4) demonstrated hemolysis had no impact on 5-ASA quantification.

In the opinion of the reviewer, (b) (4) response is adequate.

2. Specificity of N-acetyl-5-ASA in plasma failed to meet acceptance criteria in runs (run #1 and 4), and could not confirm specificity during the validation. In addition, the firm failed to provide justification for its failure.

In their response to Form FDA-483, (b) (4) acknowledged this observation and suggested that the reason for failure of the specificity experiments was due to 5-ASA in the N-acetyl-5-ASA reference standard. To confirm this hypothesis, (b) (4) repeated the experiment with freshly weighed N-acetyl-5-ASA and analyzed for both N-acetyl-5-ASA and 5-ASA. (b) (4) demonstrated that no inter-conversion of parent and metabolite occurred under the analytical and storage conditions. They suggest that the small amounts of 5-ASA found in run #1 and #4 chromatograms was due to an impurity in the N-acetyl-5-ASA reference standard instead of decomposition or non-specificity.

In the opinion of the reviewer, (b) (4) response is adequate.

3. Failure to apply the changed chromatographic integration parameters in 2 samples in runs #54 and 74 to all samples in the respective runs

In their response to Form FDA-483, (b) (4) acknowledged this observation and noted that the change in the estimated concentrations was about 4% for run #54 and about 2% for run #74. (b) (4) is of the opinion that this change will have no effect on the BE outcomes.

In the opinion of the DBGLPC reviewer, the OCP reviewer should confirm the BE outcomes after considering the changed re-integration parameters in run #54 and #74.

4. The bioanalytical report contained the text "frozen stability has been proven for 287 days in human

plasma at -80 degrees," however firm failed to provide the report containing long-term freezer stability data to the agency.

In their response to Form FDA-483, (b) (4) explained that an additional report on stability for 377 days at -80°C and 38 days at -20°C was in the possession of the sponsor at the time of inspection. The report was finalized on December 14, 2012 and attached to (b) (4) response.

In the opinion of the reviewer, (b) (4) response is adequate and this observation will have no impact on study outcomes.

5. Calibration and maintenance procedures for LC-MS/MS instruments to include the auto-sampler and LC pumps are inadequate in that they do not assure maintenance and/or calibration within certain dates. For example, (b) (4) #16 was due for (b) (4) maintenance on 11/7/12 and has not been conducted. In addition, the required maintenance was not performed for (b) (4) #14 between 10/1/12 and 12/3/12.

In the opinion of the reviewer, this observation will have no impact on study outcomes as lapses in maintenance occurred several months after complete analysis of the study samples.

Conclusions:

Following evaluation of the inspectional findings and (b) (4) response, the DBGLPC reviewer recommends the following:

- The data generated from the following samples cannot be assured:
 - Subject 507345/ (b) (6) Period 1, Sample 24 hr
 - Subject 507355/ (b) (6) Period 4, Sample 4 hr
 - Subject 507355/ (b) (6) Period 4, Sample 6 hr
 - Subject 507376/ (b) (6) Period 2, Sample 36 hr
 - Subject 507393/ (b) (6) Period 1, Sample 2 hr
 - 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.

Sripal R. Mada, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

VAI - Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX

FEI: 3006724658

NAI - Comprehensive Clinical Development, Fort Myers, FL

FEI: 3007613146

NAI - Comprehensive Clinical Development, Miramar, FL

FEI: 3006116374

VAI - [REDACTED] (b) (4)

cc:

OSI/Moreno

OSI/DBGLPC/Taylor/Dejernet

OSI/DBGLPC/BB/Haidar/Skelly/Mada

OND/ODE3/DGIEP/Davis/Barley/Griebel

OCP/DCP3/Bashaw/Apparaju

ORA/NYK-DO/Mendiola

ORA/DAL-DO/Lorenz

ORA/FLA-DO/Stegman

Draft: SRM 01/07/2013

Edit: MFS 01/07/2013; WHT 01/08/2013

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FACTS: 1453828

ATTACHMENT: 1

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/s/

SRIPAL R MADA
01/08/2013

WILLIAM H TAYLOR
01/08/2013

MEMORANDUM

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

DATE: October 02, 2012

TO: Director, Investigations Branch
Florida District Office (FLA-DO)
555 Winderley Place
Suite 200
Maitland, FL 32751

Director, Investigations Branch
New York District Office (NYK-DO)
158-15 Liberty Avenue
Jamaica, NY 11433

Director, Investigations Branch
Dallas District Office (DAL-DO)
4040 N. Central Expressway
Suite 300
Dallas, TX 75204

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2012, High Priority PDUFA, Pre-Approval Data
Validation Inspection** Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 204-412
DRUG: Mesalamine Delayed Release Capsules,
400 mg
SPONSOR: Warner Chilcott Company LLC
U.S. AGENT: Warner Chilcott (US), LLC,
100 Enterprise Drive, Rockaway, NJ
07866

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. A DBGLPC scientist with specialized knowledge will

participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGLPC upon receipt of this assignment to arrange scheduling of the inspection. Following identification of the investigator, background material will be forwarded directly. **This inspection should be completed by November 15, 2012 to meet the PDUFA review due date.**

Please DO NOT identify the application type or number, the studies to be inspected, the drug name, or the names of the study investigators prior to the start of inspection. The information will be provided to the sites at the inspection opening meetings.

Please also note that this inspection will be conducted under the Bioresearch Monitoring Compliance Program CP 7348.001 and not conducted under CP 7348.811 (Clinical Investigators).

At the completion of inspection, please send a scanned copy of the completed sections A & B to Dr. Sam Haidar and the DBGLPC point of contact (POC) listed at the end of this memo.

Study Number: PR-08210
Study Title: "A Study to Assess the Relative Bioavailability of Two WC3045 Formulations in Healthy Subjects, Study PR-08210"

Study Period: 18 November 2011 to 15 March 2012
(252 Subjects enrolled and 238 completed the study)

Clinical Site #1: Worldwide Clinical Trials Drug Development
(# of subjects: Solutions (FEI#: 3006724658)
Not Specified) 2455 N.E. Loop 410, Suite 150
San Antonio, TX 78217
Tel: +1 210 635 1584
Fax: +1 210 635 1646
Contact Person: Debbie Miksch

Clinical Site #2: Comprehensive Clinical Development
(FEI#: 3006116374)
(# of subjects: 3400 Enterprise Way
Not Specified) Miramar, FL 33025
Tel: +1 954 266 1000 Ext 1256
Fax: +1 954 266 1015
Contact Person: Umu Kamara

Clinical Site #3: Comprehensive Clinical Development
(FEI#: 3007613146)
(# of subjects: 3745 Broadway Ave, Suite 100
Not Specified) Fort Myers, FL 33901
Tel: +1 239 461 8655
Fax: +1 954 461 8601
Contact Person: Maria Bernard

Background: This was a multi-center (3 clinical sites), open-label, randomized, single-dose, replicate-treatment, 4-period, 2-sequence, 2-formulation crossover study conducted in 252 healthy male and female volunteers.

Study Objective: To assess the relative bioavailability of mesalamine delayed-release capsules (400 mg, test product), relative to Asacol (mesalamine) delayed-release tablets, 400 mg, (reference). Both investigational products were manufactured by Warner Chilcott Deutschland GmbH.

Please audit the reports of all subjects at each site included in the study. The subject records in the NDA submission should be compared to the original documents at the firm. Include description of your findings in the EIR.

SECTION A

RESERVE SAMPLES: This is a bioequivalence study and the site conducting the study (i.e., each investigator) is responsible for randomly selecting and retaining reserve samples from shipments of drug products provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal

Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993)
specifically addresses the requirements for bioequivalence
studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's Guidance for Industry, Handling and
Retention of BA and BE Testing Samples (May 2004), that clarifies
the requirements for reserve samples

(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.**
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the a third party is independent from the sponsor, the manufacturer and packager. In an event reserve samples are not retained or not adequate in quantity; please notify the POC immediately.**
- Please get a written assurance from the clinical Investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, remained in custody of investigator or responsible person at the site and they were stored under conditions specified in accompanying records. Document the signed and dated assurance (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit.
- Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Benjamin Westenberger, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101
Phone: (314) 539-3869

SECTION B

Data Audit Checklist

- Evidence of under-reporting of AEs identified?_____
 - Evidence of inaccuracy in data capture?_____
 - Presence of 100% of signed and dated informed consent forms obtained according to regulations:_____
 - Reports for 100% of subjects audited:_____
 - Number of subjects screened at the site:_____
 - Number of subjects enrolled at the site:_____
 - Number of subjects completing the study:_____
 - Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms:_____
 - Confirm that the clinical assessments were conducted in a consistent manner and in accordance with protocol-defined requirements:_____
 - Number of subject records reviewed during the inspection:_____
 - SOPs were strictly followed during study conduct:_____
 - Examine correspondence files for any sponsor- or monitor-requested changes to the study data or report:_____
 - Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations if any, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents and case report forms for dosing, **whether the randomization schedule was followed for dosing of subjects**, etc.)
 - Comments if any:
-
-

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Analytical Site:



Contact Person:

Sample Analysis: December 27, 2011 to March 1, 2012

Methodology: LC/MS-MS

Extraction Method: Protein Precipitation

Analytes Assayed: inosalicylic Acid (5-ASA)

Internal Standard:



Matrix: Human Plasma

Anticoagulant: K₂EDTA

Special Conditions: Plasma samples were prepared on ice.

Please confirm the following during the inspection:

- All pertinent items related to the analytical method used for the measurement of 5-Aminosalicylic Acid concentrations in human plasma should be examined.
- The accuracy of analytical data provided by the sponsor in the NDA submissions should be compared with the original documents at the site.
- The method validation and the actual assay of the subject plasma samples, the variability between and within runs, demonstration of at least one accuracy and precision in matrix using standards and QCs prepared from separate stocks, QC accuracy and precision during sample analysis, subject samples were analyzed within the established storage stability.
- Use of freshly made calibrators and/or freshly made QCs for stability evaluations during pre-study method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays and if relevant stability criteria like

**freeze thaw cycles sufficiently covered stability of
reanalyzed subject samples.**

In addition to the standard investigation involving the source documents, the files of correspondence between the analytical sites and the sponsor should be examined for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions and questions may be provided by DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further follow-up instructions before the inspection and also regarding any data anomalies or questions noted during review of study report. ORA investigator should contact DBGLPC POC for inspection related questions or clarifications.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA-483. Please forward written response as soon as you receive to Dr. Sam Haidar and POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

DBGLPC POC:

Gopa Biswas, Ph.D.
(301) 796-4167
Email: gopa.biswas@fda.hhs.gov

CC:

CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Biswas/Mada/Dejernett/CF
OND/ODEIII/DGIEP/Anissa Davis/Stacy Barley
OTS/OCP/DCPIII/Bashaw
ORA/SW-FO/DAL-DO/DAL-IB/SAN-TX/Joel Martinez

ORA/SW-FO/DAL-DO/DAL-IB/Susan M. Turcovski/Bias
ORA/SE-FO/FLA-DO/Kathleen Sinninger /Torres
ORA/NE-FO/NYK-DO/Laurence Daurio/Linda Sacco/ Thomas Hansen
Draft: GB 09/26/2012
Edit: AD 10/02/2012, SHH 10/2/2012
OSI: BE6381; O:\BE\assigns\bio204412.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB
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/s/

GOPA BISWAS
10/02/2012

SAM H HAIDAR
10/03/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA# 204412

Application Type: New NDA

Name of Drug: WC3045 (mesalamine) Delayed-Release Capsules, 400mg

Applicant: Warner Chilcott Company, LLC

Submission Date: 07/31/2012

Receipt Date: 08/01/2012

1.0 Regulatory History and Applicant's Main Proposals

Warner Chilcott Company, LLC, submitted a new drug application which provides for a new dosage form, mesalamine delayed-release capsule, with the following proposed indication: The treatment of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC.

Warner Chilcott (US) LLC has worked closely with the FDA to address concerns related to the potential safety of dibutyl phthalate (DBP) as an excipient in Asacol products. The Sponsor developed a new formulation and a new dosage form (WC3045 capsules) in which dibutyl phthalate (DBP) in the tablet enteric coating is replaced with the plasticizer dibutyl sebacate (DBS).

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 60-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 15, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Selected Requirements of Prescribing Information (SRPI)

Comment:

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment: *Sponsor did not capitalize drug name in the last sentence.*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- N/A** 12. All text must be **bolded**.
Comment:
- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.
Comment: *There is only one dosage form- capsule.*

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *However, the Sponsor has not submitted a Patient Label. This information will be requested.*

YES

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *However, Sponsor's references are in all caps and should be in title case*

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A

42. All text is **bolded**.

Comment:

N/A

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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 clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

Comment:

YES Patient Counseling Information

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

ANISSA A DAVIS
09/28/2012

STACY R BARLEY
09/28/2012

BRIAN K STRONGIN
09/28/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204412 BLA# N/A	NDA Supplement #: S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: (b) (4) Established/Proper Name: WC3045 (mesalamine) delayed-release capsules Dosage Form: Capsules Strengths: 400mg		
Applicant: Warner Chilcott Company Agent for Applicant (if applicable): Warner Chilcott (US) LLC		
Date of Application: 7/30/2012 Date of Receipt: 8/1/2012 Date clock started after UN:		
PDUFA Goal Date: 2/1/2013	Action Goal Date (if different):	
Filing Date: 9/30/2012	Date of Filing Meeting: 9/12/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): For the treatment of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 26,093 & NDA 019651				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		x		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid (7/25/12) <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>x</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>x</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>x</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>x</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			Module 2.4 & Module 4 not included in application (cross reference to NDA 19-651)
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	X			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #			X	
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	X			

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>		X		Although a Partial Waiver for pediatric studies (<5yrs old); Deferral of Peds Study (studies being conducted in NDA 21-830), a pediatric plan was not included. This will be requested from the applicant.
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>		X		
<p><u>BPCA (NDAs/NDA efficacy supplements only):</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Proprietary name (b) (4) submitted on 8/7/12 and withdrawn on 9/26/12.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			Consult forwarded on 8/28/12
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			There is no PPI submitted
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Consult submitted to OSE on 8/23/12
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>			X	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/10/12 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9/12/12

BLA/NDA/Supp #: NDA 204412

PROPRIETARY NAME: (b) (4) (proposed)

ESTABLISHED/PROPER NAME: Mesalamine

DOSAGE FORM/STRENGTH: 400mg capsules

APPLICANT: Warner Chilcott Company, LLC [c/o Warner Chilcott (US), LLC]

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the treatment of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC

BACKGROUND: Warner Chilcott (US) LLC has worked closely with the FDA to address concerns related to the potential safety issue of dibutyl phthalate (DBP) as an excipient in Asacol products. The Sponsor developed a new formulation (WC3045 capsules) in which dibutyl phthalate (DBP) in the tablet enteric coating is replaced with the plasticizer dibutyl sebacate (DBS) and the tablet in the encapsulated. NDA 204412 provides a new dosage form, mesalamine delayed-release capsules which are indicated for the treatment of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stacy Barley; Anissa Davis	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Sue Chih Lee		N
Clinical	Reviewer:	Marjorie Dannis	Y
	TL:	Anil Rajpal	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Sandyha Apparaju	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sruthi King	N
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Hitesh Shroff	N
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Ann Tobenkin	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees	Nitin Patel (OSC RPM); Andrew Mulberg; Donna Griebel; Joyce Korvick		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain: However, missing English translation regarding Master and executed Batch records (IR issued on 9/19/12)</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p> <ul style="list-style-type: none"> the scientific rationale and data to support partial waiver (e.g. epidemiologic information and use data for Asacol and other mesalamine products in pediatric patients). an annotated version of label with exact changes(from label of reference drug product) clearly documented 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> <ul style="list-style-type: none"> Due to the lack of a food effect study, there will be restrictive language in regard to dosing if the NDA is approved 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIostatISTICS</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: no safety concerns	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: CMC Comments- none</p> <p>Biopharmaceuticals Comments</p> <ul style="list-style-type: none"> We recommend that you evaluate if alcohol induces dose dumping for your product. First, you should conduct the in vitro alcohol induced dose dumping testing. Depending on the result of this testing you may have to follow-up with an in vivo alcohol-dose dumping study. <p>The following points should be considered during the evaluation of the in vitro alcohol induced dose dumping of your MR product:</p> <ul style="list-style-type: none"> Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile. The following alcohol concentrations for the in vitro dissolution studies are recommended in the currently proposed media: 0%, 5%, 10%, 20%, and 40%. The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours. The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference). The report with the complete data (i.e., individual, mean, SD, comparison plots, f2values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided for review. 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES

<p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO								
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO								
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO								
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter								
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter								
REGULATORY PROJECT MANAGEMENT									
<p>Signatory Authority: TBD (either Donna Griebel, Andrew Mulberg, Joyce Korvick)</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 11/29/12</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <table border="1" data-bbox="251 1707 1302 1877"> <tr> <th colspan="2" style="background-color: yellow;">GOAL DATES</th> </tr> <tr> <td>Primary Reviews Due</td> <td>12/28/12</td> </tr> <tr> <td>Secondary Reviews Due</td> <td>1/4/13</td> </tr> <tr> <td>Labeling/REMS/PMR-PMC Comments to</td> <td>1/7/13</td> </tr> </table>		GOAL DATES		Primary Reviews Due	12/28/12	Secondary Reviews Due	1/4/13	Labeling/REMS/PMR-PMC Comments to	1/7/13
GOAL DATES									
Primary Reviews Due	12/28/12								
Secondary Reviews Due	1/4/13								
Labeling/REMS/PMR-PMC Comments to	1/7/13								

Sponsor		
CDTL Review Due		1/11/13
PDUFA Date		February 1, 2013

Milestone Meetings	
Filing Meeting	9/12/12
Planning Meeting	9/27/12
Mid-Cycle Meeting	11/29/12
PeRC <i>PeRC Paperwork Due: 12/10/12</i>	12/19/12
Wrap-up Meeting	1/7/13

Team Meetings	
1	10/22/12
2	11/8/12
3	12/11/12
4	1/3/13

Labeling Meetings	
Labeling Planning Mtg (SEALD)	12/5/12
1	12/5/12
2	12/18/12
3	1/3/13
4	1/10/13
5	1/16/13
6	1/24/13
7	

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): see disciplinary comments above

	<p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ANISSA A DAVIS
09/27/2012

STACY R BARLEY
09/27/2012

BRIAN K STRONGIN
09/28/2012