# OFFICE OF CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 204412/ S-003 | Submission Date(s): September 10, 2013 |
| Brand Name | Delzicol |
| Generic Name | Mesalamine Delayed Release Capsules |
| Reviewer | Sandhya Apparaju, Ph.D. |
| Team Leader | Sue Chih Lee, Ph.D. |
| OCP Division | DCPIII |
| OND Division | DGIEP |
| Sponsor | Warner Chilcott |
| Relevant IND(s) | 26093 |
| Submission Type | Prior Approval Efficacy Supplement |
| Formulation; Strength(s) | Delayed Release Capsules; 400 mg |
| Indication | Ulcerative Colitis (UC) |

## 1 Executive Summary

### 1.1 Recommendation

Division of Clinical Pharmacology III, Office of Clinical Pharmacology finds NDA 204412/S-003 to be acceptable from a Clinical Pharmacology perspective.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Asacol® (NDA 19-651) and Asacol HD® (NDA 21-830) delayed release tablets of 400 and 800 mg mesalamine, respectively have been approved for use in adults for the treatment of mildly to moderately active UC and moderately active UC, respectively.

With the approval of Asacol HD in 2005, the sponsor was required to fulfill a PREA requirement of conducting a study in pediatrics and developing an age appropriate formulation. With the submission of a pediatric efficacy supplement NDA 21830/Supplement-006 on December 21, 2012, the sponsor fulfilled this PREA requirement by providing results from a phase 2 dose ranging trial and a phase 3 trial in pediatric UC patients 5- 17 years of age. The supplement was approved on October 18, 2013.

While the PREA requirement was issued under the NDA for Asacol HD® (800 mg; 21-830), the pediatric trials used Asacol® (400 mg delayed release tablets; NDA 19-651) as

the age appropriate formulation. Therefore Asacol HD labeling did not include pediatric dosing information. In parallel, sNDA for Asacol 400 mg tablets submitted on May 21, 2013 was also approved on October 18, 2013 and that labeling included pediatric dosing information as derived from the pediatric efficacy trials submitted to NDA 21830.

To address the Agency's concern related to the potential safety issue of dibutyl phthalate (DBP) as an excipient in Asacol products, Warner Chilcott developed a new formulation (WC3045 capsules) in which dibutyl phthalate (DBP) in the tablet enteric coating is replaced with the (b) (4) dibutyl sebacate (DBS) (b) (4) Based on communications held with the agency during the drug development, an NDA was submitted on August 1, 2012 that included results from a single dose bioequivalence study comparing the test (WC3045 capsules) and reference (Asacol 400 mg) formulations in a fully replicate crossover design, and utilizing the reference-scaled BE approach for highly variable drugs, along with special in vitro dissolution data. Data submitted demonstrated bioequivalence of the test and reference mesalamine formulations under the conditions studied (fasting) for the primary PK endpoints Cmax, AUC0-tldc as well as a partial AUC parameter AUC8-48. The NDA for Delzicol was therefore approved on February 1, 2013 in adults for UC. Delzicol has since replaced Asacol 400 mg in the market.

At the time of approval of Delzicol, the approval letter included required pediatric studies under PREA, as it was a new formulation. Given the bioequivalence of Delzicol 400 mg delayed release capsules and Asacol 400 mg delayed release tablets which have demonstrated efficacy in pediatric patients under NDA 21830/S-006, the sponsor was advised that the labeling for Delzicol can be updated to include pediatric indication and dosing for UC based on the results from pediatric trials using Asacol 400 mg.

In this regard, this prior approval efficacy supplement 003 was submitted on September 10, 2013 and provided updated Delzicol labeling to include pediatric UC indication and dosing information.

Because the approved Delzicol capsules are large compared to Asacol 400 mg tablets used in the Clinical trials and there is no information regarding the swallowability of these capsules in younger children, DGIEP in consultation with PMHS and PeRC has determined that the pediatric approval of Delzicol will be limited to children 12 years and above. Thus the PREA requirement issued at the time of Delzicol would be completely fulfilled once a pediatric formulation suitable for children younger than 12 years of age has been developed.

**Conclusions:** Division of Clinical Pharmacology III, Office of Clinical Pharmacology has reviewed the proposed labeling changes for Delzicol (NDA 204412/S-003) and found them to be acceptable with minor revisions. Please refer to the final approved labeling in DARRTs.

---

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

---

/s/

---

SANDHYA K APPARAJU
02/20/2014

SUE CHIH H LEE
02/20/2014