CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203634Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 14, 2013
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA # Supplement #	***NDA 203634***
Applicant Name	Santarus, Inc.
Date of Submission	December 14, 2011 (submitted) / December 16, 2011 (received)
PDUFA Goal Date	January 16, 2013 (includes 3-month extension due to Major Amendment)
Proprietary Name / Established (USAN) Name	Uceris® / budesonide
Dosage Forms / Strength	9 mg tablet
Proposed Indication(s)	Induction of remission in patients with mild to moderate UC
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Statistical Review	Milton Fan, PhD Michael Welch, PhD
Medical Officer Review	Marjorie Dannis, MD
Pharmacometrics	Nitin Mehrotra, Ph.D.
Clinical Pharmacology	Kristine Estes, PhD Sue Chi Lee, PhD.
Biopharmaceutics	Elsbeth Chikhale
OPDP	Eunice Chung-Davies Kendra Jones
DMPP	Latonia Ford
DMEPA	Anne Tobenkin Denise Baugh
CMC	Raymond Frankewich
QT-IRT	Monica Fiszman
Pharmacology Toxicology Review	Dinesh Gautam Sushanta Chakder, Ph.D.
OSI	Susan Leibenhaut, MD
Project Manager	Kevin Bugin
CDTL Review	Anil Rajpal, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

In this NDA supplement, the applicant proposes to market budesonide (Uceris) for the following indication in adults:

1) for induction of remission in patients with active mild to moderate ulcerative colitis

Budesonide 9 mg tablets (Uceris) contains a synthetic corticosteroid with topical anti-inflammatory properties, weak mineralocorticoid activity, and undergoes substantial first pass elimination. This extensive first pass metabolism by the liver may ensure little systemic availability, which may result in less glucocorticoid (GCS)-related side effects compared to conventional systemically available steroids. It is enteric-coated to provide delayed release characteristics at the appropriate pH, to protect the drug substance from gastric acid and enzyme degradation. The tablet core contains 9 mg of budesonide and a mixture of polymers that further control the extended release characteristics of the drug substance, along with other excipients. In this New Drug Application (NDA), the Applicant pursues the approval of budesonide with labeling for "… for induction of remission in patients with active mild to moderate ulcerative colitis." This is a 505(b)(2) application based on Entocort EC (NDA 21-324) as the reference drug.

The Applicant presents data from two phase 3 controlled studies, CB-01-02/01 and CB-01-02/02 submitted in support of the NDA. The key design features of these trials are reproduced below. These are further described in the Clinical review of Dr. Dannis and CDTL memorandum of Dr. Rajpal:

Table 1: Study Design Characteristics of Pivotal Clinical Development Program

Study	Region / Country	Design	Population	DB Treatment Period	Treatment Arms
CB-01-02/01	North America and India	R, DB, PC	▪ active mild or moderate UC*	8 weeks	➢ Uceris 6 mg/day (n=126) ➢ Uceris 9 mg/day (n=127) ➢ Asacol 2.4 g/day[#] (n=127) ➢ Placebo (n=129)
CB-01-02/02	Europe	R, DB, PC	▪ active mild or moderate UC*	8 weeks	➢ Uceris 6 mg/day (n=128) ➢ Uceris 9 mg/day (n=128) ➢ Entocort EC 9 mg/day[†] (n=126) ➢ Placebo (n=129)

R: Randomized; DB: Double-blind; PC: Placebo-controlled
* UCDAI ≥ 4 and ≤ 10
[#]Asacol two 400 mg tablets TID
[†] Entocort EC 3 x 3 mg/day

There were a number of concerns raised by the Statistical and Clinical reviewers during the review of this application, including protocol violations potentially affecting interpretation of efficacy, change in primary analysis population, placebo subjects with normal histology and safety concerns regarding glucocorticoid safety. These concerns resulted in multiple internal discussions regarding approvability. Disagreement between the Clinical and Statistical reviewers was hinged on the definition of the disease population but Drs. Rajpal and Dannis recommended an Approval action. Substantial evidence of efficacy was demonstrated based on the results in the mITT analysis population (i.e., Sponsor's ITT analysis population) of each of the two studies (Studies CB-01-02/01 and CB-01-02/02) but not in the "all randomized" population. An issue that was integral to this discussion is the role of histological diagnosis of ulcerative colitis (UC) and its impact on the definition of a mITT population. Several critical issues affecting the level of statistical evidence included an unplanned sample adjustment and the interpretation of the analysis population. In addition protocol conduct was characterized by major violations of the ITT population, which necessitated a review of its impact on analysis population (ITT versus mITT) to assess effectiveness. Despite disagreement with the Primary Statistical Reviewer, Dr. Fan, the Statistical Team Leader, Dr. Welch, is of the opinion that in toto there "appears to be adequate documentation supporting the sponsor's change to the primary analysis population to include subjects with positive histology at baseline, and the introduction of bias due this change is not evident. Base on this analysis population, both studies show statistically significant results….The overall level of statistical evidence of efficacy based on both studies is in this reviewer's opinion, sufficient to support a recommendation for product approval by the Clinical team." The issues are discussed further in **Section 7 Clinical**.

In the past, a number of new molecular entities (NMEs) studied and approved for an indication in UC have been characterized with heterogeneous approaches, focusing on the inclusion criterion of defining histological evidence of disease activity as part of the disease definition. This issue is referred to in the clinical review of UCERIS 9 mg tablets, in which Dr. Dannis states, "the efficacy of budesonide 9 mg in inducing remission was established by the results of the two randomized, double-blind, double-dummy, placebo-controlled, parallel group, multi-center studies (CB-01-02/01 and CB-01-02/02). Each of these studies demonstrated that budesonide 9 mg was statistically significantly superior to placebo in inducing clinical remission, the primary endpoint of both studies. A stringent definition of the primary endpoint was applied in CB-01-02/01 and CB-01-02/02, incorporating symptomatic (clinical), endoscopic, and Investigator-based criteria into the definition of remission. According to the Sponsor, the ITT population was defined prospectively in the Statistical Analysis Plan (SAP) for each study. It included all randomized patients who received at least one dose of study drug, had no major entry criteria violations, had no major GCP violations, and had histological evidence of active UC disease at baseline. The timing of the Sponsor's changes in analysis populations was not ideal, and presented challenging review issues. However, according to this reviewer, the Sponsor's ITT population does represent the appropriate population for the primary analyses, as it includes only patients who have active, mild/moderate UC and includes only reliable patient data."

Recent registration trials for indications in UC, there have been diverse approaches, regarding inclusion criterion of histological evidence of disease activity. In this clinical development

program, the disease definition of UC included both endoscopic and histological evidence of disease activity. In contrast to other approved indications in UC, Lialda™ as treatment for the maintenance of remission in UC, Remicade™ and Humira™ as treatment for the induction of remission in moderately to severely active UC, respectively required biopsy confirmed evidence of active UC. Approval of Apriso™ for the maintenance of healing of UC and AsacolHD™ did not require biopsy-confirmed evidence of UC. Results from trials conducted for [redacted] (b) (4) ™ were analyzed with histology not consistent with ulcerative proctitis, a milder form of UC.

For trials in UC, the confirmation of histological evidence of disease activity is critical for its diagnosis, as well as for excluding other related inflammatory bowel disease conditions or conditions mimicking active UC. Histology confirms presence of idiopathic inflammation, including distorted crypt architecture or other features of chronicity, lamina propria inflammation, crypt abscess, and neutrophils in the surface epithelium. The presence of a granuloma on rectal biopsy or perianal disease such as fissure or tags would suggest Crohn's disease and exclude a diagnosis of UC. For example, the ACT 1 trial of Remicade™ specified inclusion criteria as: ”Have had ulcerative colitis of at least 3 months’ duration at screening, confirmed by the biopsy taken at screening” and ACT 2 (Remicade™) : “Had ulcerative colitis of at least 3 months' duration at screening, confirmed by the biopsy taken at screening. If the screening biopsy result was not yet available, a previous biopsy result confirming UC must be available in the subject's medical records and reviewed prior to receiving study agent.”[1] The trials for Humira™ cited “Diagnosis of active UC confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy during the Screening Period, with exclusion of infection.”

It is the opinion of this Signatory that the inclusion criteria for clinical trial populations with UC require confirmation of histological evidence of disease activity. This is critical moving forward to maintain a consistent approach to disease definition of UC. In this review, these issues shall be discussed further, as they relate to the definition of the ITT, Sponsor’s ITT and modified ITT populations and are resolved to support labeling of Uceris 9 mg tablets for this indication.

Despite these issues, I conclude and agree with the Clinical Reviewer, CDTL and Statistical Team Leader for approval of the NDA for Uceris 9 mg tablet. The data provided offer sufficient data to support efficacy and safety for the proposed use of Uceris for for induction of remission in patients with active mild to moderate ulcerative colitis based on the body of evidence from this study. The Statistics Team leader also provided the critical perspective that “there appears to be adequate documentation supporting the sponsor’s change to the primary analysis population to include subjects with positive histology at baseline, and the introduction of bias due to this change is not evident. Based on this analysis population, both studies show statistically significant results, each with an effect size of about 10%. Study 02 has the GCP violation issues as well as the apparent randomization imbalance in subjects with normal histology; for these reasons, this study should be considered supportive to the principle trial, study 01. The overall level of statistical evidence of efficacy based on both studies is, in this reviewer’s opinion, sufficient to support a recommendation for product approval by the

[1] These inclusion criteria were reproduced from relevant protocols concerning Remicade™ reviewed for its NDA approval.

Clinical team." Despite the issues surrounding the interpretation of the analysis populations, the data supports effectiveness of the product.

In summary, I have concluded that there is sufficient evidence of clinical benefit supported by the data in this application to establish that Uceris 9 mg tablets are effective and safe for the treatment of patients with mild to moderately to severely active ulcerative colitis. My review will focus on the salient issues related to this risk/benefit assessment.

2. Background

Budesonide has been previously approved for the indication of management of a type of inflammatory bowel disease, Crohn's disease and marketed as Entocort™. Uceris is formulated as a delayed and extended release tablet to deliver budesonide directly into the colon and then slowly disperse the budesonide over a period. The tablet, coated with an acid-resistant polymer film, breaks down at or above pH 7.0, which is the normal pH in the terminal ileum. The acid-resistant coating allows the tablet to pass through the acidic condition of the stomach without significant decomposition. It is in the ileum where budesonide is released from the tablet core. The tablet core contains budesonide with specific polymers that provide for the extended release of budesonide throughout the colon.

Understanding the disease definition of ulcerative colitis (UC) as a clinico-pathological disease characterized by both gross and microscopic inflammation of the colon, affecting the anus to the cecum is important. The American College of Gastroenterology Practice Guidelines for Management of Ulcerative Colitis clearly states that "in a patient presenting with persistent bloody diarrhea, rectal urgency, or tenesmus, stool examinations and sigmoidoscopy or colonoscopy **and biopsy (bold added for emphasis)** should be performed to confirm the presence of colitis and to exclude the presence of infectious and noninfectious etiologies. Characteristic endoscopic **and histological (emphasis added)** findings with negative evaluation for infectious causes will suggest the diagnosis of UC."[2] It is even more critical to appreciate that certain histological features are more indicative of ulcerative colitis, which include the presence of loss of vascular pattern, granularity, friability, and ulceration. These involve the distal rectum circumferentially and completely. Histological features of UC that may distinguish from infectious etiologies include the characteristic mucosal separation, distortion and atrophy of crypts; chronic inflammatory cells in the lamina propria, preferential homing of neutrophils to the crypt epithelium, increased number of lymphocytes and plasma cells at the crypt bases, shortfall of crypts not reaching to the mucosal mucosa and basal lymphoid aggregates. Paneth cell metaplasia and villous mucosal architecture are also helpful in differentiating diagnoses[3]. As noted in the Clinical review by Dr. Dannis, the Applicant used the Saverymuttu Scale acquired from colonoscopic biopsies to describe the histopathological features of UC (Table 2). This scoring system reflects critical elements of UC disease, which is important to the definition of the datasets in this application and particularly the protocol violations in study conduct.

[2] Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. Korbluth A, Sachar DB and the Practice Parameters Committee of the ACG. Amer J Gastroenterol 2010;105:501-523.
[3] ibid

Table 2: Saverymuttu Scale: reproduced from the Clinical review of Dr. Dannis

Histopathological Observations		Score
Enterocytes	Normal	0
	Loss of Single Cells	1
	Loss of Groups of Cells	2
	Frank Ulceration	3
Crypts	Normal	0
	Single Inflammatory Cells	1
	Cryptitis	2
	Crypt Abscesses	3
Lamina Propria Mononuclear Cells	Normal	0
	Slight Increase	1
	Moderate Increase	2
	Marked Increase	3
Lamina Propria Neutrophils	Normal	0
	Slight Increase	1
	Moderate Increase	2
	Marked Increase	3
	Total Score	**0-12**

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In this application, the diagnosis of UC fulfilled both endoscopic and histological criteria. The role of histological confirmation of UC disease activity was particularly important for the interpretation of efficacy data and definition of the ITT and mITT populations. This issue is discussed below. The pertinent Rates of Clinical Remission mITT Population (Study CB-01-02/01) and CB-01-02/02) are reproduced below from the CDTL memorandum:

Table 3. Rates of Clinical Remission mITT Population (Study CB-01-02/02)

	Placebo N=121	Budes. MMX 9 mg N=123	Budes. MMX 6 mg N=121	Asacol 2400 mg N=124
Remission: n (%)	9 (7.4)	22 (17.9)	16 (13.2)	15 (12.1)
95% CI	2.8, 12.1	11.1, 24.7	7.2, 19.3	6.4, 17.8
Difference between active and placebo		10.4	5.8	4.7
95% CI		2.2, 18.7	-1.8, 13.4	-2.7, 12.1
p-value		0.0143*	0.1393	0.2200

Source: Table 14.2-1.1.1

Abbreviation: Budes., budesonide; CI: confidence interval

Notes: The denominator for calculating percentages was the number of patients in each treatment group in the ITT population. Patients with missing data that precluded determination of remission were analyzed as not having achieved remission in these analyses (i.e., worst case). All p-values were based on the Chi-square test; comparisons of budesonide MMX and placebo were conducted at the $\alpha = 0.025$ level of significance and the comparison of Asacol and placebo were conducted a the $\alpha = 0.05$ level of significance. The study was not powered to show statistical significance for Asacol versus budesonide MMX.

* Value is statistically significant at the $\alpha = 0.025$ level.

Table 4. Rates of Clinical Remission mITT Population (Study CB-01-02/02)

	Placebo N=89	Budes. MMX 9 mg N=109	Budes. MMX 6 mg N=109	Entocort EC 9 mg N=103
Remission, n (%)	4 (4.5)	19 (17.4)	9 (8.3)	13 (12.6)
95% CI	0.2, 8.8	10.3, 24.6	3.1, 13.4	6.2, 19.0
Difference vs. placebo		12.9	3.8	8.1
95% CI		4.6, 21.3	-3.0, 10.5	0.4, 15.9
p-value[d]		0.0047*	0.2876	0.0481†

Source: Tables 14.2-1.1.1

Abbreviations: Budes., budesonide; CI: confidence interval.

Notes: Patients with missing data that precluded determination of remission were analyzed as failures in these analyses (i.e., worst case). The denominator for calculating percentages was the number of patients in each treatment group in the ITT population. All p-values were based on the Chi-square test, with α = 0.025 for comparisons of budesonide MMX and placebo and α = 0.05 for the comparison of Entocort and placebo. The study was not powered to show statistical significance for Entocort EC versus budesonide MMX.

* Value is statistically significant at the α = 0.025 level.

† Value is statistically significant at the α = 0.05 level.

Tables reproduced from CDTL Memorandum, Dr. Rajpal

The statistical and clinical considerations affecting determination of efficacy are discussed below in section 7.

3. CMC

The reader is referred to the CMC review of Raymond Frankewich, dated November 9, 2012, and should be for complete information. Although the CMC Review noted that there were deficiencies identified in the NDA that precluded approval of this application, the Addendum to the CMC Review noted that those deficiencies had been resolved. The Reviewer recommends approval.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Reviewer recommends an Approval action based on the non-clinical review of the information submitted in the NDA. The Nonclinical Reviewer agreed with the Applicant is proposed labeling for the following sections:

- Section 8.1 of Label (Pregnancy)
- Section 13.1 of Label (Carcinogenesis, Mutagenesis, Impairment of Fertility)

The following section of labeling should be deleted as per the reviewer:

- Section 13.2 of Label (Animal Toxicology and/or Pharmacology)

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the review of Dilara Jappar, dated December 19, 2012. My review focuses on the pertinent aspects of clinical pharmacological aspects of exposure as they relate to corticosteroid effects, and hypothalamic-pituitary and adrenal (HPA) suppression issues,

particularly to this formulation. This Signatory underscores the concern of potential greater HPA suppression of Uceris as noted in Dr. Rajpal's CDTL memorandum. In the Clinical Pharmacology review, Dr. Jippar has noted that Uceris 9 mg results in HPA axis suppression. Forty-seven percent, (47%) of patient who were treated with Uceris 9 mg for 4 weeks and 79% of patients who were treated with Uceris 9 mg for eight consecutive weeks had an abnormal response to the ACTH stimulation test, indicating HPA axis suppression. The Clinical Pharmacology Reviewer noted the following limitations to the comparison with the Entocort EC data (in addition to being a cross-study comparison): (1) the study with Uceris 9 mg was based on a very limited number of patients, n= 14. (2) It is possible that the criteria to categorize an abnormal ACTH response differed between the two studies (it is not clear what criteria were used in the Entocort EC study). These data are supplemented by Dr. Jappar's presentation to OCP Rounds on December 13, 2012 demonstrating that the bioavailability of Uceris is higher than a comparator product, Pulmicort (Table 5, reproduced below):

Table 5. Features of Exposure of Varying Budesonide Formulations

Budesonide Product /formulation/NDA #	Approved Dose	Cmax(nmol/L)/ dose	AUC (nmol.h/L)/ dose
Pulmicort Inhalation powder NDA 20441	Adults: 200-400 ug BID Ped (6 & up): 200 -400 ug BID	Not available	Not available
Pulmicort Flaxaler Inhalation powder NDA 21949	Adults: 180-360 ug BID Ped (6 & up): 180-360 ug BID	0.6 / 180 ug 1.6 /360 ug 3.32 /4*180 ug	9.5 /4 x 180 ug
Pulmicort Respules Inhalation suspension NDA 20929	Ped : (1-8 years): 0.5-1 QD 0.25-0.5 mg BID No adult indication	2.6 /1 mg (in ped)	10.9 / 1mg (in ped)
Rhinocort Aqua Nasal Spray NDA 20746	Adults: 64 ug QD (256 ug max) Ped (6 & up): 64 ug QD (128 ug max)	0.3 / 128 ug 1 / 400 ug	4.2 / 400 ug
Symbicort Aerosol Inhalation NDA 21929	Adults: 80-160 ug BID Ped (12 & up): 80-160 ug BID	1.36/ 4*160 ug (640) 3.9 / 8*160 ug (1280) 6.1/12*160 ug (1920) 1.8/ 12*40 ug (480) 3.2/ 12*80 ug (960) 5.4/12*160 ug (1920)	4.2/ 4*160 ug (640) 14.6 /8*160 ug (1280) 19.0 /12*160 ug (1920) 6.0/ 12*40 ug (480) 10.8/ 12*80 ug (960) 19.8/ 12*160 ug (1920)
Entocort EC Oral Capsule NDA 21324	Adults: 6-9 mg QD	5 / 9 mg (label) 3.6 /9 mg (in this submission)	30 / 9 mg (label) 31 /9 mg (in this submission)
Uceris	**Adults: 9 mg QD**	**3.1 /9 mg**	**38 /9 mg**

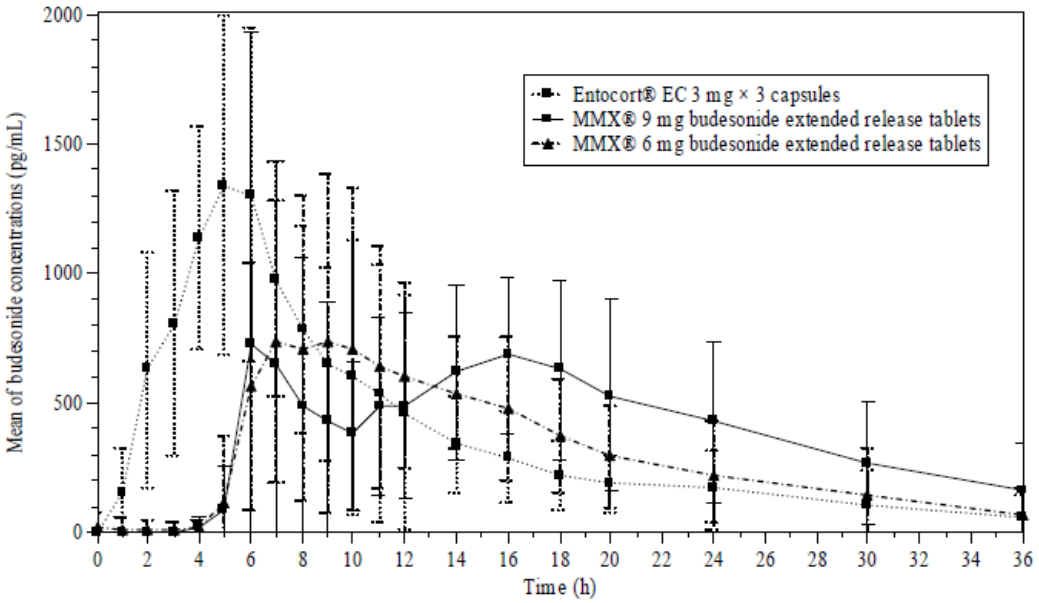
The data above reflect a higher exposure compared to other inhalation or nasal spray budesonide products at the respective approved doses.

Dr. Jappar commented that the possible higher HPA axis suppression potential of Uceris 9 mg versus Entocort EC 3 x 3 mg might be due to the prolonged exposure of budesonide in this new formulation compared to Entocort EC (see Table 6 and Figure 1 below).

Table 6. Plasma budesonide PK parameters of varying doses and formulations

Plasma budesonide PK parameters - Mean ± SD (CV%)			
	MMX™ 9 mg (T1)	MMX™ 6 mg (T2)	Entocort® EC 3 x 3 mg
PP-population (N=12)			
T_{max}(h)	13.3 ± 5.9 (44.5)	11.4 ± 5.1 (44.4)	4.8 ± 1.4 (28.6)
C_{max} (pg/mL)	1348.8 ± 958.8 (71.1)	1158.5± 532.4 (46.0)	1555.9 ± 588.0 (37.8)
AUC_{0-t} (pg/mLxh)	13555.9 ± 7816.9 (57.7)	10818.3 ± 4401.6 (40.7)	13394.6 ± 5983.0 (44.7)
$AUC_{0-\infty}$ (pg/mL×h)	16431.2 ± 10519.8 (64.0)	11533.6 ± 4738.5 (41.1)	14057.0 ± 6378.7 (45.4)
C_{max} (pg/mL) / dose	149.9 ± 106.5 (71.1)	193.1 ± 88.7 (46.0)	172.9 ± 65.3 (37.8)
AUC_{0-t} (pg/mLxh) / dose	1506.2 ± 868.5 (57.7)	1803.0 ± 733.6 (40.7)	1488.3 ± 664.8 (44.7)
$t_{1/2}$(h)	8.2 ± 3.7 (44.7)	6.6 ± 2.4 (36.8)	7.7 ± 1.8 (23.1)
MRT (h)	21.4 ± 6.8 (31.5)	17.0 ± 5.7 (33.7)	11.6 ± 2.7 (23.1)

Figure 1. Mean Budesonide plasma concentration profiles following oral administration of Uceris 9 mg tablets (T1), Uceris 6 mg tablets (T2) and Entocort® EC 3 x 3 mg capsules



Dilara Jappar takes the figure above from the Clinical Pharmacology Review.

Uceris and Entocort EC have comparable AUC and Cmax exposures but different PK profiles- see Figure 1, above. Uceris might have higher potential for HPA axis suppression but this is not confirmed with submitted studies. These conclusions are based on cross-study comparisons of the ACTH stimulation test, revealing 79% patients in 9 mg Uceris with abnormal response versus 54% patients on Entocort as noted above. Supporting data include morning Cortisol levels revealing that budesonide 9 mg had greater amount of decrease (-101 nmol/L) in the morning plasma cortisol levels compared to Entocort (-47.0 nmol/L) after 8 weeks of treatment. In addition, there were a greater percentage of patients in the Budesonide 9 mg group, who had abnormally low morning cortisol level compared to Entocort after 8

weeks of treatment (25.8% vs. 13.3%). The absolute conclusion of greater HPA suppression is suggestive but it is not definitive.

The appropriate labeling of this formulation, as done for all corticosteroid formulations for other indications, i.e., pulmonary, dermatological, describe the potential for adverse drug reactions secondary to HPA suppression. The FDA uses standardized, common language for the potential to cause HPA axis suppression as a Warning/Precaution in ALL of the corticosteroid labels regardless of route and systemic exposure. The results of HPA axis studies are also labeled in **Section 12 Clinical Pharmacology** of the drug label. Uceris is characterized as having higher total systemic exposure and significant first-pass hepatic metabolism. The impact of these pharmacokinetic features will be important to elucidate in the pediatric population, which is more susceptible to HPA axis suppression exerting effects on growth velocity. These issues are described further, below in **Section 10 Pediatrics**.

Despite the evidence that Uceris may be associated with higher HPA axis suppression, there are not new pharmacokinetic signals that preclude appropriate labeling of the product. The Signatory agrees with the Approval recommendation of the Clinical Pharmacology reviewer.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Uceris is not an antimicrobial agent.

7. Clinical/Statistical-Efficacy

I do concur with the reviews of Drs. Dannis, Welch and Rajpal who have disagreed with Dr. Fan regarding the demonstration of efficacy of Uceris 9 mg tablets for the induction treatment of UC. The reader is referred to Dr. Rajpal's CDTL memorandum for further review and complete information of historical efficacy data, related to clinical trial and exposure data related to Uceris. This Signatory will focus on the critical issues identified by the Statistical and Clinical reviewers and included the following concerns, potentially, affecting efficacy analyses:

A. Normal Histology or Infectious Colitis at Entry and Change in the Primary Analysis Populations after Study Enrollment: Dr. Dannis in the review of Regulatory history reviews the timeline of the changes to the Statistical Analysis Plan and study conduct. The Sponsor's ITT population included all randomized patients who received at least one dose of study drug, excluding those with major entry criteria violations, major GCP violations, and normal histology at baseline. From Tables 7 and 8 below, exclusions from the Sponsor's ITT Analysis Populations, (Studies CB-01-02/01 and CB-01-02/02) revealed 20 patients (3.9%) (17 patients with normal histology at entry and 3 patients with infectious colitis at entry) in CB-01-02/01. For CB-01-02/02 twenty-nine of the 101 excluded patients had both normal histology at baseline and major GCP violations, and are thus included in both categories. Tables 7 and 8 below describe these data.

Table 7. Exclusions from the Sponsor's ITT Analysis Population (Study CB-01-02/01)

Category of Exclusion	Placebo	Uceris 9 mg	Uceris 6 mg	Asacol 2.4 g	Total
"True" ITT	129	127	126	127	509
Sponsor's ITT* (mITT)	121	123	121	124	489
Patients Excluded from Sponsor's ITT	8 (5.5%)	4 (3.1%)	5 (4.7%)	3 (2.4%)	20 (3.9%)
Infectious Colitis at Entry[#]	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	3 (0.6%)
Normal Histology at Entry[†]	6 (4.7%)	3 (2.4%)	5 (3.9%)	3 (2.4%)	17 (3.3%)

*The Sponsor's ITT population included all randomized patients who received at least 1 dose of study drug, excluding those with major entry criteria violations, major GCP violations, and normal histology at baseline.
[#]Infectious colitis at entry was a major entry criteria violation.
[†]Normal histology at entry was defined as all available biopsies from a colonoscopy had a total Sayermattu Score ≤ 1 (corresponding to a Histological Activity Grade of 0) (see Appendix 3 of CDTL memorandum)
(Table above is modified from Table 8 on Page 54 of the Study Report for Study CB-01-02/01.)
Reproduced from CDTL memorandum

Table 8. Exclusions from the Sponsor's ITT Analysis Population (Study CB-01-02/02)

Category of Exclusion	Placebo	Uceris 9 mg	Uceris 6 mg	Asacol 2.4 g	Total
"True" ITT	129	128	128	126	511
Sponsor's ITT* (mITT)	89	109	109	103	410
Patients Excluded from Sponsor's ITT	40 (31.0 %)	17 (13.5 %)	19 (14.8%)	23 (18.3%)	101 (19.8%)
Treated, but not randomized	1 (0.8%)	1 (0.8%)	0	0	2 (0.4%)
Infectious Colitis at Entry[#]	0	1 (0.8%)	0	0	1 (0.2%)
Major GCP Violation	20 (15.5%)	9 (7.1%)	9 (7.0%)	12 (9.5%)	50 (9.8%)
Normal Histology at Entry[†]	33 (25.6%)	12 (9.5%)	16 (12.5%)	16 (12.7%)	77 (15.1%)

*The Sponsor's ITT population included all randomized patients who received at least 1 dose of study drug, excluding those with major entry criteria violations, major GCP violations, and normal histology at baseline.
[#]Infectious colitis at entry was a major entry criteria violation.
[†]Normal histology at entry was defined as all available biopsies from a colonoscopy had a total Sayerymuttu Score ≤ 1 (corresponding to a Histological Activity Grade of 0) (see Appendix 3 of CDTL memorandum)
(Table above is modified from Table 8 on Page 55 of the Study Report for Study CB-01-02/02.)
Reproduced from CDTL memorandum

The Primary Statistics Reviewer concluded that for each study, the sponsor's ITT analysis (based on the exclusion of all patients with normal histology at baseline) should be considered a subgroup analysis that is hypothesis generating (rather than the primary analysis) because the sponsor's ITT analysis population was not "clearly pre-specified". Dr Fan noted that for each study, the sponsor's ITT analysis population was pre-specified in the SAP but not the protocol. Although the SAP was finalized before database lock, the sponsor's ITT analysis population was introduced in the SAP after study enrollment. The Statistical Team leader disagreed and noted that there is precedent in FDA for performing efficacy analysis on a subset of the ITT population, namely histology positive subjects in the trial. As this Signatory has stated earlier, histological evidence of disease activity is critical and needed for correct diagnosis of UC. As stated by Dr Welch, the performance of biopsy to diagnose UC is performed prior to randomization and does not invalidate the randomization. There is no evidence to support Dr Fan in his supposition of the converse and this Signatory does not concur with his recommendation.

B. <u>Major GCP Violations</u>:

There were no patients with major GCP violations in Study CB-01-02/01 but there was exclusion of four sites with major GCP Violations (in Study CB-01-02/02): The Primary Statistics Reviewer noted that the exclusion of four sites with major GCP violations contributes to the difficulty in interpretation of results from Study CB-01-02/02. In the course of any study conduct, major GCP violations lead to questioning the veracity of the efficacy data. The Sponsor in this case predefined in the SAP the exclusion of data from sites associated with GCP violations. As noted by Dr Welch in his review that the "removal of protocol violators from the primary analyses is inconsistent with statistical review practice as protocol violators would be removed from a per-protocol data set not an ITT or modified ITT data set." However, it is critical to note that in this case or any case of clinical trial conduct, mischaracterization of a population as having the disease when they do not would necessarily cause confusion and misinterpretation of data and therefore result in a Type II error. As discussed by Drs. Dannis and Rajpal, there is allowance for such practice in ICHE9, which namely states that there are a limited number of circumstances that might lead to the exclusion of randomized subjects from the full analysis set. These include failure to satisfy major entry criteria, failure to take at least one dose of trial medication and lack of any data post randomization. Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:

- The entry criterion was measured prior to randomization
- The detection of the relevant eligibility violations can be made completely objectively
- All subjects receive equal scrutiny for eligibility violations; data should not be unblinded prior to this scrutiny
- All detected violations of the particular entry criterion are excluded

Dr Welch agrees that the removal of such sites may be justified, but the analyses with and without the sites support the drug's efficacy. As Signatory, I agree with these assessments and support approval of Uceris 9 mg tablets.

C. Disproportionate Numbers of Placebo Subjects with Normal Histology at Baseline in Study CB-01-02/02):

The Primary Statistics Reviewer commented that more patients were excluded from the placebo group compared to the Uceris 9 mg group in Study CB-01-02/01 (5.5% vs. 3.1%) and Study CB-01-02/02 (31.0% vs. 13.5%) (mostly due to normal histology at baseline in Study CB-01-02/02), and concluded that the results from each of the studies (particularly Study CB-01-02/02) may be biased in favor of the Uceris 9 mg group. As noted by Dr. Welch, there is a larger than expected number of placebo subjects with normal histology. There is no concrete evidence that the randomization process was flawed or erroneous. Critically since the Sponsor's mITT and the primary analysis, population excluded normal histology-as discussed above- this therefore does not create any concerns for this Signatory.

In toto, the results for each of the three populations ["true" ITT analysis population, baseline histology positive population, and modified ITT population (i.e., sponsor's ITT analysis population)] are summarized by study in the two tables below. The Sponsor's ITT population is herein, referred to as the mITT population and included all randomized patients who received at least one dose of study drug, excluding those with major entry criteria violations,

major GCP violations, and normal histology at baseline. The data described in Tables 8 and 9 below illustrate the specific clinical remission rates by Analysis populations of CB-01-02/01 and CB-01-02/02:

Table 8. Clinical Remission Rates by Analysis Population - Study CB-01-02/01

Population	Treatment Arms				Uceris 9 mg - Placebo
	Placebo	Uceris 9 mg	Uceris 6 mg	Asacol 2400 mg	
"True" ITT*	**10.9%** (14/129)	**17.3%** (22/127)	15.1% (19/126)	12.6% (16/127)	**6.4%** (p=0.1365)
Histology Positive[#]	**8.2%** (10/122)	**18.5%** (23/124)	13.8% (17/123)	12.1% (15/124)	**10.3%** (p=0.0238)
mITT[†]	**7.4%** (9/121)	**17.9%** (22/123)	13.2% (16/121)	12.1% (15/124)	**10.5%** (p=0.0143)

*"True" ITT Population results from Statistics Review by Milton Fan Page 20 (p value based on chi-squared test).
[#]Histology Positive Population results from Statistics Review by Milton Fan Page 27 (p-value based on Fisher's exact test).
[†]mITT (i.e., Sponsor's ITT) Population results from CSR Study CB-01-02/01 Table 17 (p value based on chi-squared test).
Copied from CDTL Memorandum, Dr. Rajpal.

Table 9. Clinical Remission Rates by Analysis Population - Study CB-01-02/02

Population	Treatment Arms				Uceris 9 mg - Placebo
	Placebo	Uceris 9 mg	Uceris 6 mg	Asacol 2400 mg	
"True" ITT*	**14.0%** (18/129)	**17.2%** (22/128)	12.5% (16/128)	15.9% (20/126)	**3.2%** (p=0.4746)
Histology Positive[#]	**6.3%** (6/96)	**16.7%** (19/114)	8.0% (9/112)	14.5% (16/110)	**10.4%** (p=0.0308)
mITT[†]	**4.5%** (4/89)	**17.4%** (19/109)	8.3% (9/109)	12.6% (13/103)	**12.9%** (p=0.0047)

*True ITT Population results from Statistics Review by Milton Fan Page 43 (p value based on chi-squared test).
[#]Histology Positive Population results from Statistics Review by Milton Fan Page 44 (p-value based on Fisher's exact test).
[†]mITT (i.e., Sponsor's ITT) Population results from CSR Study CB-01-02/02 Table 17 (p value based on chi-squared test).
Copied from CDTL Memorandum, Dr. Rajpal.

What is critically important is the clearly demonstrated dose-response relationship particularly in the clinical remission rates observed in the histology positive subgroup of the ITT population. Demonstration of an increased response from the ITT population is consistent with our understanding of the pathophysiology and the mechanism of action of Uceris 9 mg tablets for induction of remission. This is not an unexpected result based on my earlier discourse on disease definition and the response of disease to treatment. Clearly, the response rate observed with Uceris is not in question. The issues of removal of patients with protocol violations and the impact on the definition of the efficacy population have been discussed above, and in Section 9 below.

For discussion of the specifics of the protocol violations and site inspections, review of Section 11.1 *Office of Scientific Investigations (OSI) Audits* in the CDTL memorandum is recommended. The primary comparisons were based on all randomized subjects with positive diagnosis of UC. In this case, both studies show significant results, each with an effect size close to 10%. Study 02 has the protocol violation issues as well as an imbalance between the placebo and active treatment groups in the number of subjects with normal histology. This does not necessarily imply a particular bias in efficacy results, since the colonic biopsies were done before treatment assignment as discussed above despite the difference in opinion. The Signatory agrees with Drs. Rajpal, Dannis and Welch who have an Approval recommendation.

8. Safety

Budesonide and synthetic glucocorticosteroid products are generally associated with the following adverse reactions, Warnings and Precautions as identified in the current labeling. Adverse reactions typical of systemic glucocorticosteroids include adrenal suppression, sleep and mood disturbance, acne, striae, hirsutism, proximal myopathy, glucose intolerance, hypertension, narrow angle glaucoma, cataracts, bone loss, aseptic necrosis and reduced growth velocity. These adverse reactions are generally dependent on dose, treatment time, concomitant and previous glucocorticosteroid intake, and individual sensitivity. Other adverse reactions reported in clinical trials include dyspepsia, muscle cramps, tremor, palpitations, blurred vision, skin reactions, menstrual disorders, hypokalemia, and behavioral changes.

From the review of safety, data associated with SAEs reported for patients in the primary analysis group are presented in the table below. SAEs occurred in 3% (25/1020) of patients. SAEs occurred in a similar percentage of patients in all treatment groups (2% to 3%), with the exception of the Entocort group, which had a lower incidence (<1%). SAEs were most frequently reported in the gastrointestinal disorders SOC (2%); the incidence was similar across all treatment groups (<1% to 2%). SAEs in all other SOCs were reported in <1% of all patients. SAEs occurring in more than one patient by PT were UC (1%) and treatment failure (<1%). The incidence of UC was similar in the Budesonide 9 mg (2%) and placebo (2%) groups and lower in the Budesonide 6 mg (<1%), Asacol (<1%), and Entocort (<1%) groups. Treatment failure was reported as an SAE in two patients; both were in the Budesonide 9 mg group and reproduced in Table 10 below:

Table 10. Safety Characteristics

	Phase III Randomized, Double-blind					
System Organ Class Preferred Term	Placebo N=258 n (%)	MMX 9 mg N=255 n (%)	MMX 6 mg N=254 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)	Total N=1020 n (%)
Patients with any SAE	8 (3.1)	7 (2.7)	5 (2.0)	4 (3.1)	1 (0.8)	25 (2.5)
Gastrointestinal Disorders	4 (1.6)	4 (1.6)	4 (1.6)	2 (1.6)	1 (0.8)	15 (1.5)
Colitis Ulcerative	4 (1.6)	4 (1.6)	2 (0.8)	1 (0.8)	1 (0.8)	12 (1.2)
Diarrhoea	0	1 (0.4)	0	0	0	1 (0.1)
Enterocolitis	0	0	1 (0.4)	0	0	1 (0.1)
Gastric Ulcer	0	0	0	0	1 (0.8)	1 (0.1)
Large Intestine Perforation	0	1 (0.4)	0	0	0	1 (0.1)
Nausea	0	0	1 (0.4)	0	0	1 (0.1)
Pancreatitis	0	0	0	1 (0.8)	0	1 (0.1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.4)	1 (0.4)	0	1 (0.8)	0	3 (0.3)
Colon Cancer	0	1 (0.4)	0	0	0	1 (0.1)
Renal Cell Carcinoma	0	0	0	1 (0.8)	0	1 (0.1)
Signet-Ring Cell Carcinoma	1 (0.4)	0	0	0	0	1 (0.1)
General Disorders and Administration Site Conditions	0	2 (0.8)	0	0	0	2 (0.2)
Treatment Failure	0	2 (0.8)	0	0	0	2 (0.2)
Infections and Infestations	1 (0.4)	0	0	0	0	1 (0.1)
Pelvic Abscess	1 (0.4)	0	0	0	0	1 (0.1)
Nervous System Disorders	0	0	1 (0.4)	0	0	1 (0.1)
Cerebrovascular Accident	0	0	1 (0.4)	0	0	1 (0.1)
Psychiatric Disorders	1 (0.4)	0	0	0	0	1 (0.1)
Personality Disorder	1 (0.4)	0	0	0	0	1 (0.1)
Renal and Urinary Disorders	0	0	1 (0.4)	0	0	1 (0.1)
Urge Incontinence	0	0	1 (0.4)	0	0	1 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.4)	0	0	0	1 (0.1)
Asthma	0	1 (0.4)	0	0	0	1 (0.1)
Skin and Subcutaneous Tissue Disorders	0	0	0	1 (0.8)	0	1 (0.1)
Pyoderma Gangrenosum	0	0	0	1 (0.8)	0	1 (0.1)
Vascular Disorders	1 (0.4)	0	0	0	0	1 (0.1)
Deep Vein Thrombosis	1 (0.4)	0	0	0	0	1 (0.1)

Overall, the most common individual glucocorticoid effects were mood changes and sleep changes (4% each). Review of the individual events showed that the frequency of events was similar or lower with Budesonide 9 mg when compared with placebo (Table 11 below):

Table 11. Potential Glucocorticoid Effects in the Primary Analysis Group

	Phase III Randomized, Double-blind					
Glucocorticoid Effect	Placebo N=258 n (%)	MMX 9 mg N=255 n (%)	MMX 6 mg N=254 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)	Total N=1020 n (%)
Overall	27 (10.5)	26 (10.2)	19 (7.5)	15 (11.8)	17 (13.5)	104 (10.2)
Moon face	4 (1.6)	3 (1.2)	3 (1.2)	2 (1.6)	2 (1.6)	14 (1.4)
Striae rubrae	2 (0.8)	0	0	0	0	2 (0.2)
Flushing	3 (1.2)	0	1 (0.4)	2 (1.6)	1 (0.8)	7 (0.7)
Fluid retention	3 (1.2)	2 (0.8)	3 (1.2)	3 (2.4)	0	11 (1.1)
Mood changes	11 (4.3)	9 (3.5)	10 (3.9)	3 (2.4)	6 (4.8)	39 (3.8)
Sleep changes	12 (4.7)	7 (2.7)	10 (3.9)	1 (0.8)	9 (7.1)	39 (3.8)
Insomnia	8 (3.1)	6 (2.4)	6 (2.4)	2 (1.6)	5 (4.0)	27 (2.6)
Acne	5 (1.9)	6 (2.4)	2 (0.8)	6 (4.7)	3 (2.4)	22 (2.2)
Hirsutism	0	1 (0.4)	0	1 (0.8)	1 (0.8)	3 (0.3)

Adapted from Tables 6 and 7 (p 20/57) Section 2.7.4 Summary of Clinical Efficacy and copied from Dr Dannis review

The absence of long-term complications of glucocorticoid effects is reassuring of product safety-see Dr. Dannis review, pages 54-56. The concerns though of short-term pediatric safety will be addressed in the pediatric PMR as discussed below. No new safety issues concerning Uceris have been raised from this development program.

9. Advisory Committee Meeting

There was no advisory committee for this application.

A Senior Leadership discussion with Statistics was held and included, Sue Jane Wang, Deputy Director, Mathematical Statistician, Associate Director, Statistics; Stephen Wilson, Director, Statistics; Michael Welch, Statistical Team leader; Lisa Lavange, Director of Office of Biostatistics; DGIEP Clinical team representatives, including Marjorie Dannis, Anil Rajpal, Donna Griebel, Division Director, DGIEP and this Signatory. Dr Wang concurred that "mITT analyses have been used to approve drugs but does not include GCP violators, which is generally included in the per-protocol analysis population. Most mITT includes those who have at least one post-baseline measurement, whereas true ITT includes all randomized patients." The issues of identifying the ITT, mITT analysis populations have been fully vetted in Section 7 of this review and Senior leadership supports the Approval decision.

10. Pediatrics

Concerns over growth impairment in pediatric patients who would have exposure to Uceris are related to the potential greater HPA axis suppression. These issues and deliberations have been discussed at PERC. Despite the current data supporting greater HPA suppression with this new formulation of budesonide, assessment of growth studies was not mandated as a PMR for Entocort™ that has similar bioavailability and PK characteristics as Uceris, Unlike the pulmonary indications for budesonide, UC is treated acutely with recurrence of treatment but pulmonary disease is often treated with chronic exposure. According to Peter Starke, MD, Deputy Division Director of Pulmonary Division, the FDA uses use standardized, common

language for the potential to cause HPA axis suppression as a Warning/Precaution in ALL of the corticosteroid labels regardless of route and systemic exposure. The results of HPA axis studies are labeled in the Clinical Pharmacology section of the label. Second, aside from individual susceptibility, the biggest factor in HPA axis would be the total systemic exposure. For a gut drug, that is likely most dependent upon whether there is significant first pass hepatic metabolism, although that would only be a factor when one wishes to compare across different steroids rather than between different formulations of the same steroid.

These pharmacological differences may manifest differently in the pediatric population and potential impairment of growth in children may be mitigated by the intermittent exposure to Uceris, since it is not approved for chronic use. In addition the PMR mandated in this approval will characterize first the efficacy and safety of short-term use of Uceris. All subsequent trial results will be labeled for the potential of safety concerns related to corticosteroids in the label in **Section 6.**.

11. Other Relevant Regulatory Issues

The Sponsor certified that all of the studies contained in the NDA submission were performed in compliance with guidelines for Good Clinical Practice (GCP) and were conducted under the supervision of an IRB, or IEC equivalent, with adequate informed consent procedures. According to the Sponsor, twenty-seven investigator site audits were performed throughout studies CB-01-02/01 and CB-01-02/02. Critical audit findings related to Good Clinical Practice (GCP) that could adversely affect product quality, the rights, safety or well being of subjects and/or the quality and/or integrity of the data were noted at four investigator sites (from Study CB-01-02/02 only). These critical GCP violations (see Appendix A of the Clinical Review for detailed description) led the Sponsor to conclude that all efficacy data from these four sites should be excluded (a total of 50 patients). Consequently, all the patient results for these four sites were excluded from the ITT population. Due to this finding, the Division of Scientific Investigations (DSI) performed inspections of two domestic and four foreign sites. Only preliminary results of these inspections were available at the time of the Clinical Review (5 December 2012). However, four sites were VAI, two sites were NAI and none was OAI (data unreliable). See Appendix C of the Clinical Review for further details. The Clinical Reviewer agreed that the patient results (which would not be reliable data) for these four sites should be excluded from the efficacy analyses.

12. Labeling

12.1 Proprietary Name

For complete information, see the DMEPA Proprietary Name Review by Anne Tobenkin, dated April 16, 2012, and DMEPA Proprietary Name Reviews by Denise Baugh, dated July 25, 2012, and December 11, 2012.

DMEPA concluded in the review dated April 16, 2012, that the proprietary name of “Uceris” was acceptable. This was communicated to the Applicant in the Proprietary Name Request

Conditionally Acceptable Letter dated April 17, 2012, along with a statement that the proposed proprietary name of "Uceris" will be re-reviewed 90 days prior to the approval of the NDA.

DMEPA conducted re-evaluations of the proposed proprietary name of "Uceris" (see reviews dated July 25, 2012, and December 11, 2012); again, DMEPA concluded that the proprietary name of "Uceris" was acceptable.

12.2 Office of Prescription Drug Promotion (OPDP) Comments

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name (Uceris) is acceptable from a promotional perspective. This is documented in the Proprietary Name Review by Anne Tobenkin, dated April 16, 2012, and Proprietary Name Reviews by Denise Baugh, dated July 25, 2012 and December 11, 2012.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The main revisions to the Applicant's proposed Physician Labeling are summarized below:

- Dosage and Administration (Section 2 of Label): The recommendation for repeated (b) (4) of Uceris (originally proposed by the Applicant) was removed.
- Drug Interactions (Section 7 of Label): A sub-section entitled "Inhibitors of Gastric Acid Secretion" was added that included the following statement: "Since the dissolution of the coating of UCERIS is pH dependent, the release properties and uptake of the compound may be altered when UCERIS is used after treatment with gastric acid reducing agents (e.g., PPIs, H2 blockers and antacids)."
- Clinical Studies (Section 14 of Label): In the description of the study design, the total number of patients enrolled (not including GCP violations) (i.e., 970 patients) was stated, but an additional statement was added describing the primary analysis population ("Eight-hundred ninety-nine of these patients had histology consistent with active UC; this was considered the primary analysis population.") The sub-section entitled (b) (4) (originally proposed by the Applicant) was removed.

In addition to these revisions, additional revisions were negotiated with the Applicant. Many of these revisions are based on recommendations from the DMPP Patient Labeling Review, the OPDP Labeling Review, and the OPDP Patient Labeling Review. The reader is referred to each of these reviews for complete information.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the carton and container labels. They made a number of recommendations that were communicated to the Applicant on December 14, 2012 (see DMEPA Label and Labeling Review by Anne Tobenkin, dated April 10, 2012).

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:

All of the review disciplines recommended the product for approval. This Signatory concurs with the approval recommendation.

13.2 Risk Benefit Assessment:
All of the review disciplines recommended the product for approval. This Signatory concurs with the approval recommendation.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:

No special post marketing risk management activities are recommended for this Application.

Recommendation for other Postmarketing Requirements and Commitments
A post marketing required pediatric study under PREA has been communicated to the Applicant for the current application, with the following language for the Approval Letter:

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

We are waiving the pediatric study requirement for ages 0 to <5 years because necessary studies are impossible or impracticable based on the incidence and prevalence of ulcerative colitis in the pediatric population of this age cohort (b) (4)

We are deferring submission of your pediatric study for ages 5 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been initiated or completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required post marketing study. The status of this post marketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1997-1 An 8-week randomized, double blind, placebo-controlled trial in children 5 to 17 years of age with active, mild to moderate ulcerative colitis. The trial will evaluate pharmacokinetics (PK), efficacy for induction of remission, and safety of at least 2 doses of Uceris (budesonide). The effects of 8 weeks of Uceris (budesonide) on the HPA axis will be assessed.

Final Protocol Submission:	09/2013
Trial Completion:	06/2016
Final Report Submission	09/2016

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

/s/

ANDREW E MULBERG
01/14/2013
Division Deputy Director Review