CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203634Orig1s000

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 # 203634
Product Name:

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	09/2013
	Study/Trial Completion:	06/2016
	Final Report Submission:	09/2016
	Other:	N/A

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 application was presented to the Pediatric Research Committee (PeRC) on November 28, 2012.

The PeRC agreed with the Division to grant a partial waiver in patients birth to <5 years of age because studies are impossible or highly impractical because there are too few patients with disease/condition to study. The PeRC also agreed with the Division to grant a deferral in patients 5 to 17 years of age because the product is ready for approval in adults.

PeRC recommendations included the following: (1) Request the sponsor to adjust the timelines for studies; (2) Conduct of a growth study is not needed; (3) Evaluate this product for (b) (5); (4) Include assessment of PK in the study to ensure similar exposures; (5) The sponsor should be encouraged to submit a revised Pediatric Plan.

Other items discussed included the following: (1) The Division currently believes that the tablet is appropriate for use down to five years of age, but there will need to be additional discussion between the Division and the Sponsor about the development of an age-appropriate formulation. (2) Committee members questioned if it may have been possible for pediatric studies in this age group to have already been completed for this product. (3) (b) (5)

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."

See the description in Section 1.

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.

See the description in Section 1.

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

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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/

KEVIN B BUGIN
01/10/2013

ANIL K RAJPAL
01/11/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 203634	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Uceris Established/Proper Name: budesonide Dosage Form: tablet Strengths: 9 mg		
Applicant: Santarus, Inc		
Date of Receipt: 12/15/2011		
PDUFA Goal Date: 01/16/2013 (with 3 month extension)	Action Goal Date (if different):	
Proposed Indication(s): induction of remission in patients with mild to moderate ulcerative colitis		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Entocort EC (NDA 021324)	See labeling: Section 2.1 Hepatic Insufficiency, Section 2.2 CYP3A4 Inhibitors, Section 4 Contraindications, Section 5 Warnings and Precautions, Section 6.2 Postmarketing Experience, Section 7 Drug Interactions, Section 8 Use in Specific Populations, Section 10, Overdosage, Section 12 Clinical Pharmacology, Section 13 Nonclinical Toxicology

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The bridging study is Study CRO-PK-06-178 (an open-label, randomized, single-center, single-dose, three-way cross-over, exploratory study in 12 healthy male and female subjects under fasting condition to compare the bioavailability and PK profile of a new MMX 9 mg budesonide extended release tablets formulation vs. the market reference formulation, Entocort® EC 3 mg × 3 capsules and vs. MMX 6 mg budesonide extended release tablets).

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Entocort EC	**NDA 021324**	**Y**

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph: **Budesonide**

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication, induction of remission in active, mild to moderate ulcerative colitis, and a new strength of 9 mg.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☒

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):
RHINOCORT NDA-020746;
SYMBICORT NDA-21929;
PULMICORT NDA 020441;
PULMICORT FLEXHALER NDA-21949;
PULMICORT RESPULES NDA-020929;
Generics available;

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): Entocort EC-Patent No: 5643602

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification*

was submitted, proceed to question #15.

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5643602
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *02/20/2012, 02/21/2012, 02/22/2012*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

KEVIN B BUGIN
01/10/2013

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

Product Title	**UCERIS (budesonide) extended release tablets, for oral use**
Applicant	Santarus, Inc.
Application/Supplement Number	NDA 203634
Type of Application	Original Submission
Indication(s)	For the induction of remission in patients with active, mild to moderate ulcerative colitis
Established Pharmacologic Class[1]	glucocorticosteroid
Office/Division	ODE III/DGIEP
Division Project Manager	Kevin Bugin
Date FDA Received Application	December 16, 2011
Goal Date	January 16, 2013
Date PI Received by SEALD	December 31, 2012
SEALD Review Date	December 31, 2012
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.

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 is 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: *This statement is not placed on the line immediately beneath the HL heading.*

Product Title

NO 10. Product title in HL must be **bolded.**

Comment: *Product title is not bolded.*

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:

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:

Selected Requirements of Prescribing Information

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

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 established pharmacologic class) indicated for (indication)".

Comment:

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.

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

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

YES 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

NO 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.

Comment: *Subsection headings 7.1 and 7.2 are missing from the TOC. Insert. Subsection 8.6 in the TOC should be "Hepatic Impairment" not "Hepatic." By regulation, 13.1 is designated as "Carcinogenesis, Mutagenesis, Impairment of Fertility" not "….and Impairment of Fertility." Delete the word "and." Also, the title* [redacted] (b) (4) *must be deleted from the TOC.*

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:

Selected Requirements of Prescribing Information

NO 32. All section headings must be **bolded** and in UPPER CASE.

Comment: *The section headings in the TOC appear in title case and are not bolded.*

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:

NO 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: *The statement is missing at the end of the TOC. Insert.*

Full Prescribing Information (FPI)

GENERAL FORMAT

NO 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment: *The heading is not bolded.*

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

Comment:

NO 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
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY

Selected Requirements of Prescribing Information

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: *Delete the word "and" from subsection heading 13.1.*

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:

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:

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:

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

YES 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
12/31/2012

LAURIE B BURKE
01/02/2013

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

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

Memorandum

Date: December 28, 2012

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

From: Kendra Y. Jones, Regulatory Review Officer,
Division of Consumer Drug Promotion (DCDP),
Office of Prescription Drug Promotion (OPDP)

CC: Eunice Chung-Davies, Regulatory Review Officer,
Division of Propfessional Drug Promotion (DPDP), OPDP

Subject: NDA 203634
OPDP labeling comments for UCERIS (budesonide) extended release tablets for oral use

---

OPDP has reviewed the proposed draft prescribing information (PI) and patient information (PPI) for UCERIS (budesonide) extended release tablets for oral use submitted for consult on January 31, 2012.

OPDP's comments on the proposed draft PI were provided on December 20, 2012, by Eunice Chung-Davies.

OPDP has no comments on the version of the proposed draft PPI sent via email by Latonia Ford (RPM) on December 21, 2012. This version of the proposed draft PPI is provided directly below.

Thank you for the opportunity to comment on this label.

If you have any questions regarding this proposed draft PPI, please contact Kendra Jones at 301-796-3917 or Kendra.jones@fda.hhs.gov.

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

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/s/

KENDRA Y JONES
12/28/2012

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: December 20, 2012

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

From: Eunice Chung-Davies, Regulatory Review Officer,
Division of Professional Drug Promotion (DPDP),
Office of Prescription Drug Promotion (OPDP)

Cc: Kendra Y. Jones, Regulatory Review Officer,
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: NDA 203634
DPDP labeling comments for UCERIS (budesonide) extended release tablets for oral use

---

DPDP has reviewed the proposed draft prescribing information (PI) for UCERIS (budesonide) extended release tablets for oral use submitted for consult on January 31, 2012.

DPDP's comments on the proposed draft PI based on the version of proposed PI via email from Kevin Bugin (RPM) on December 17, 2012, provided directly below.

OPDP's comments on the patient labeling will follow under separate cover from Kendra Jones.

Thank you for the opportunity to comment on this label.

If you have any questions regarding this proposed draft PI, please contact Eunice Chung-Davies at 301-796-4006 or Eunice.chung-davies@fda.hhs.gov.

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

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/s/

EUNICE H CHUNG-DAVIES
12/20/2012

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: December 17, 2012

TO: Kevin Bugin, Regulatory Project Manager
Marjorie Dannis, M.D., Medical Officer

FROM: Khairy Malek, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-634

APPLICANT: Cosmo Technologies Ltd. (Santarus, Inc.)

DRUG: Uceris (budesonide MMX)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Induction of Remission in Active Mild or Moderate Ulcerative Colitis

CONSULTATION REQUEST DATE: February 13, 2012

REVISED CONSULT REQUEST DATE June 21, 2012

PDUFA DATE: January 16, 2013

I. BACKGROUND:

The current treatment for ulcerative colitis (UC) is sulfasalazine and 5-aminosalisylates, but these agents are not effective for all patients. Budesonide is a moderately potent corticosteroid with low oral bioavailability due to extensive first path hepatic metabolism leading to a systemic bioavailability of 10-15%. To date budesonide has been evaluated for use in patients with inflammatory bowel disease when administered either orally as a controlled release formulation, or rectally as an enema.

A new controlled release system, MMX extended-release tablets, characterized by a multi-matrix structure that releases the active ingredient in the distal gastro-intestinal tract at a controlled rate, has been recently developed. Using budesonide in this multimatrix structure as an active ingredient 6 or 9 mg appears to be a more suitable formulation for the treatment of distal colonic lesions than existing oral budesonide formulations. Use of the MMX formulation in Phase I produced a homogenous and progressive distribution of budesonide through the colon to treat diseases located in that region such as UC and other inflammatory colorectal diseases.

Safety information obtained in a Phase II study where budesonide-MMX 9 mg was used for 8 weeks included the following adverse events: facial acne, low morning cortisol, urgency, tachycardia, headache, stomach pain, nausea, and flatulence.

Two protocols were requested for inspection by the review division:

1. CB-01 02/01, entitled “Efficacy and Safety of New Oral Budesonide MMX (CB-01-02) 6 mg and 9 mg Extended Release Tablet Formulations in Patients with Mild or Moderate Active Colitis. A Multicenter, Double-Blind, Double-Dummy, Comparative Study versus Placebo, with an Additional Reference Arm Evaluating Asacol® 2400 mg” and

2. CB-01-02/02 titled “Efficacy and Safety of Oral Budesonide MMX (CB-01-02) 6 mg and 9 mg Extended Release Tablets in Patients with Mild or Moderate Active Ulcerative Colitis. A Multicenter, Randomized, Double-Blind, Double Dummy, Comparative Study Versus Placebo with an Additional Reference Arm Evaluating Entocon® EC.”

The Ulcerative Colitis Disease Activity Index (UCDAI) was used to determine eligibility criterion and also the primary endpoint. The index consists of four components: stool frequency, rectal bleeding, mucosal appearance, and physicians’ rating of disease activity.

Sites were originally chosen for inspection by the review division on the basis of enrollment and remission rates. Sites 9004 and 1055 were chosen in the original consult. Site 9004 had a

large percentage of the patients who completed the study. The remission rate in the budesonide MMX 9 mg arm was three out of eight subjects (37.5%) and the remission rate in the placebo arm was one out of four subjects (25%). Site 1055 had the largest percentage of patients who completed the study at any site. The remission rate in the budesonide MMX 9 mg arm was two out of ten subjects (20%) and the remission rate in the placebo arm was zero out of four subjects (0%). Because the sponsor proposed to exclude the efficacy and safety data from four sites for GCP violations (Sites 1040 in Italy, Site 1106 in Russia, and Sites 1082 and 1122 in Slovakia), it was suggested that the number of inspections be increased in order to determine whether the extent of GCP violations was more widespread than stated by the sponsor. Additional sites were chosen for inspection based on numbers of subjects enrolled, whether the site had been audited by the sponsor and the results, and feasibility of completion of inspections in a timely manner. Specifically, Slovakia Site 1122 was chosen because it was a site that was audited and recommended for exclusion by the sponsor and Poland Site 1059 was chosen because it was a site that was audited by the sponsor and was not recommended for exclusion by the sponsor (see details in Section III Review of Sponsor Audit Reports). In the amendment to the NDA submitted on May 3, 2012, the sponsor stated that a sensitivity analysis was conducted to determine whether the exclusion of the efficacy data from the four sites had any impact on the results of the study. According to the sponsor, an analysis in which the subject remission data from the four sites was set to non-responder and an analysis with the remission status as reported by the sites both demonstrated the superiority of Uceris 9 mg compared to placebo.

In this clinical inspection summary (CIS), Section II is the of a review of the inspected sites in the table on page 4, Section III is a review of the audits submitted by the sponsor to the NDA on August 3, 2012, and Section IV contains OSI's conclusions based on the results of the review of the inspection reports and the audits.

II. FDA INSPECTION RESULTS (by Site):

Name of CI/ Sponsor and Location	Protocol # # of Subjects Site #	Inspection Date	Final Classification
Neil Cohen, M.D. S. Jersey Gastroenterology 406 Lippincott Dr., Suite E Marlton, NJ 08053	CB-01-02/01 10 Subjects Site 5005	August 2 to 13, 2012	VAI
Tawfik Chami, M.D. Florida Medical Clinic 38135 Market Square Zephyrhills, FL 33542	CB-01-02/01 9 Subjects Site 5003	August 6 to 8, 2012	NAI
Umesh Jalihal, M.D. Kamataka Gastroenterology Center 887 Dr. Modi Hospital, RD., Basaveshwarnagar Bangalore-Kamataka, India	CB-01-02/01 20 Subjects Site 9004	September 9 to 13, 2012	VAI
Limas Kupcinskas, M.D. Kaunas Medical University Hospital, Eiveniu 2, Kaunas, LT 50009, Lithuania	CB-01-02/02 27 Subjects Site 1055	September 3 to 9, 2012	VAI
Robert Petryka, M.D. VIVAMED, ul. Zamiejska 17, Warszawa, Poland	CB-01-02/02 17 Subjects Site 1059	September 10 to 14, 2012	NAI
Dr. Ivan Bunganic Gastro I, s.r.o. Puskinova 18, Presov, 08001 Slovakia	CB-01 02/02 22 Subjects Site # 1122	September 24 to 28, 2012	Pending (Preliminary classification VAI)
Sponsor: Cosmo Technologies Ltd./Santarus, Inc. San Diego, CA	CB-01-02/01 CB-01-02/02	November 26 to 29 and December 5, 2012	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Neil Cohen, M.D.**
   Marlton, NJ 08053

   a. **What was inspected:** The protocol studied at this site was CB-01-02/01. At this site, 13 subjects were screened, and 10 subjects were randomized. The field investigator reviewed the records of all subjects in the study including source documents and data listings.

   b. **General observations/commentary:** The first subject was consented and screened on December 10, 2008. Subject 002 (randomized to MMX 9mg) had a report of exhaustion in the diary and demonstrated a drop in Cortisol from 19.2 at Visit 2 (before study drug) to <1.0 at Visits 3, 4, and 5. The exhaustion was not reported as an adverse event. Listing 16.2.8.4. in the NDA for this subject indicates the cortisol as "low" with "No" indicated in the clinical significance column. Subject 005 (randomized to placebo) had a notation of stomach pain in the source documents, but this was not reported as an adverse event. Otherwise, there did not appear to be underreporting of adverse events. A Form FDA 483 was issued for the following violations.
      1. The protocol for Study CB-01-02/01stated that the principal investigator (PI) or subinvestigator (sub-I) should sign and date the Informed Consent Documents (ICD). Neither the PI nor the sub-I signed the ICDs for Subjects 001, 002, 003, 004, 005, 009, 010, 011, 012, and 013.
      2. The protocol for Study CB-01-02/01 stated that, before the study starts, the protocol and any written information regarding the study be provided to the patient must be approved by the Institutional Review Board (IRB). Even thought the Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ) was submitted to the IRB for approval, due to an oversight by the IRB, the IBDQ was not approved until June 3, 2009. The IBDQ was used by Subjects 001, 002, 003, 004, and 005 prior to the approval by the IRB.
      3. For two subjects cortisol levels were not taken between 8-10 AM as the protocol specifies. Subject 011 had a sample taken at 14:55 and Subject 012 had a sample taken at 14:00.
      4. The protocol specified that no antibiotics be used as concomitant medications. Four subjects used antibiotics: Subject 009 used Leviquin, Subject 011 used amoxicillin, Subject 002 used Cipro, and Subject 013 used Bactrim.

   Additional items noted in the EIR concerning study conduct:
      5. Written colonoscopy reports at Visits 1 and 5 do not consistently use the same terminology as all of the characteristics listed in the EIA table in the source documents. The FDA investigator observed no consistent correlation between the colonoscopy report and the results recorded on the EIA. The EIA table is not signed by the physician performing the colonoscopy, and there were no study notes to indicate that this was discussed with the physician. Dr. Cohen stated that, based on the colonoscopy reports which included pictures, he could correlate the two. Dr. Cohen also stated that he believed that the study coordinator and the subinvestigator performing the colonoscopy would have discussed the information.

6. Source documents did not have documentation indicating that the physician provided input to the EIA, UCDAI, and CAI assessment forms. This was not required by the protocol, but was requested in e-mails to study personnel. Dr. Cohen stated that the study coordinator would have discussed the evaluation with the sub-investigator.
7. For Subjects 001, 002, and 003, UCDAI and CAI assessments for Visit 1 were signed and dated at Visit 1, but the information was not available until Visit 2 when the subject diaries were reviewed.
8. Storage conditions are to be at 77^0F with excursions permitted down to 59^0F. The EIR and exhibits document one day of 58.5^0F and two consecutive days of temperature of 56^0F and 57.5^0F, in February 2009, and 2 consecutive days of 58.5^0F in March 2009. These isolated excursions are not likely to affect the stability of the product.

c. **Assessment of data integrity:** The protocol violations are not expected to affect the validity of the data. The lack of indication of the clinical significance of low cortisol for Subject 002 appears to be an isolated occurrence. The additional observations concerning study conduct concerned poor documentation for the screening assessment and lack of documentation as to who performed the assessments. The nature of these violations is not likely to impact data integrity. Data generated at this site can be used in support of the NDA.

2. **Tawfik Chami, M.D.**
Zephyrhills, FL 33542

a. **What was inspected:** The protocol studied at this site was CB-01-02/01. At this site, 12 subjects were screened, nine subjects were randomized, and seven subjects completed the study. Two subjects withdrew their consent. An audit of all subject records was conducted. This included subjects' source documents, laboratory values, colonoscopy results, and efficacy parameter scores which were supported by source documents.

b. **General observations/commentary:** The first subject was enrolled on August 22, 2008. An audit of all subjects' records was conducted. No significant regulatory violations were noted. The inspection reviewed subjects' source documents, laboratory values, colonoscopy results, efficacy parameters, and assessments (CAI, UCDAI). The source documents were compared with the line listings and they were supported by source documents. No violations of federal regulations were observed.

c. **Assessment of data integrity:** The data generated at this site can be used in support of the NDA.

3. **Umesh Jalihal, M.D.**
Bangalore, India

a. **What was inspected:** The protocol studied at this site was CB-01-02/01. At this site, 23 subjects were screened, 20 were randomized, 15 subjects completed the study, and five subjects withdrew. The field investigator reviewed all the study records including IRB correspondence, informed consents, monitoring, eCRFs, drug accountability records, protocol violations, and inclusion/extension criteria.

b. **General observations/commentary**: The first subject was consented and screened on November 9, 2009. The primary efficacy endpoint data for remission were verified by comparing the source documents, eCRFs, and line listings concerning achievement of remission. There was no evidence of under-reporting of adverse events. A Form FDA 483 was issued for the following violations:

1. The investigation was not conducted in accordance with the investigational plan because there is no documentation of eligibility determination in the screening day Visit 1 notes for Subjects 9004017 and 9004022.

Reviewer note: In his response letter of September 28, 2012, Dr. Jalihal pointed out that his notes are complete and contain the enumeration of eligibility criteria. It is only the statement "inclusion exclusion criteria reviewed met", that is not present for these subjects. This is not considered a significant protocol violation, and it appears that the subjects were appropriately included in the trial.

2. Failure to prepare or maintain adequate case histories:
   a. The PI Visit 1 notes were not maintained in the file for Subjects 5 and 8.
   b. The source document for Subject 1 Visit 1 Clinical Activity Index (CAI) states "number of stools weekly are <18", and a score of 0, but the Visit 1 Subject diary reports 20 stools and a CAI score of 1.
   c. For Subject 20 the source document for Visit 1 total Endoscopic Index Assessments and Score (EI) of 5 is documented; however, the eCRF states a score of 7.
   d. For Subject 22, the source document for Visit 5 CAI has a total score of 12 but the eCRF has a value of 11.

Reviewer note: In his written response of September 28, 2012, Dr. Jalihal described his office procedures concerning transcription of the office notes to account for the deficiency and the calculation of the number of stools for subject 1. He also noted that the citation "d" applied to Visit 3, not Visit 5. He noted that the EIA assessed on Visit 1 in January 2010 was later revised on re-assessment in July 2010. The e-mail communication and audit trail were included.

c. **Assessment of data integrity:** These violations do not affect the validity of the data. The data generated at this site can be used in support of the NDA.

4. **Limas Kupcinkas, M.D.**
Kaunas, Lithuania

a. **What was inspected:** The protocol studied at this site was CB-01-02/02. At this site 27 subjects were screened and randomized, and 20 subjects completed the study. The field investigator reviewed the source documents, drug accountability records, and eCRFs for the 20 subjects.

b. **General observations/commentary:** There was no under-reporting of adverse events and the primary efficacy endpoint data contained in the source diaries was compared with the eCRF and no discrepancies were noted.

1. Failure to maintain adequate and accurate records.
   a. For most of the subjects (2, 3, 4, 5, 6, 7, 8, 9, 13, 14, 16, 17, and 23) the concomitant medication mesalazino was not recorded. In his response of September 18, 2012, Dr. Kupcinskas stated that, because the protocol required that these medications be discontinued before the screening visit, he interpreted this to mean that they were not on the medication and did not enter this into the case report forms. He noted that this oversight was not mentioned to him by the sponsor monitor.

Reviewer note: This appears to be a misinterpretation of the protocol that was not corrected by the monitor and applies to subjects in all arms of the study. The review division should determine the significance of this finding.

   b. There were 34 discrepancies in data points noted concerning items in the subject diary, subject vital signs, and drug returns. Most of these were in data points such as the CAI that is a secondary endpoint, or "no temp recorded" for source document, but eCRF stating 36.6^0C. Two of these discrepancies concerned UCDAI, the primary endpoint. For Subject 018 (MMX 9mg cohort), for Visit 1 the source data stated that the stools were more than 4/day above normal frequency and the eCRF stated that the stools were 1-2/day more than normal. For Subject 015 (MMX 9mg cohort), for Visit 5, the subject marked 3-4 times greater than normal but eCRF was changed to state 1-2 times normal. In his response, the CI stated that the site will implement preventive measures to ensure more accuracy in transcription of data from source to CRF.

Reviewer note: Although there are numerous instances of transcription errors occurring, it appears that the subject diary items comprising the primary endpoint was correctly captured in all cases except for stool frequency for Subject 015. The errors above changed the stool frequency results to a more favorable outcome for study drug but did not change the overall outcome in that the subjects did not achieve remission.

2. Inspection also revealed a protocol violation in that Subject 018 and Subject 022 were enrolled with less than six month history of UC required by the protocol.

Reviewer note: Enrollment of these two subjects with less than a six month history of UC was not cited on the Form FDA 483. These deviations were included as deviations by the sponsor

in the line listings submitted to the NDA, and the dates were properly documented in the source data and the eCRF.

c. **Assessment of data integrity:** The review division should determine the significance of the omission of the prestudy medications for UC at this site. The protocol deviations were reported by the sponsor and are contained in the line listings in the NDA. Although there were numerous transcription errors between the source diaries and the eCRF, there was no significant impact on the primary efficacy endpoints. The violations observed would not affect the validity of the data. The data generated at this site can be used in support of the NDA.

5. **Robert Petryka, M.D.**
Warszawa, Poland

a. **What was inspected:** At this site, 22 subjects were screened and 17 were enrolled; 5 were screen failures. The field investigator reviewed the records of all subjects. This included informed consent, financial disclosures, drug accountability records, efficacy parameters, adverse events and patient diaries.

b. **General observations/commentary:** The first subject was screened on December 2, 2008. No violation of federal regulations was observed, and no For FDA 483 was issued.

c. **Assessment of data integrity:** (For a discussion of the sponsor's audit report of this clinical investigator site, see Section 3 page 15.) The data obtained at this site are reliable and can be used in support of the NDA.

6. **Dr. Ivan Bunganic**
Presov, Slovakia

Note: Observations noted for this inspection are based on communications with the FDA investigator and receipt of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected:** At this site, 23 subjects were screened and 22 subjects were enrolled. A total of 18 subjects completed the study. Records for 16 subjects were examined during the inspection. The review included source documents, informed consent documents, inclusion/exclusion criteria, and drug accountability records.

b. **General observations/commentary:** The first subject was randomized on March 18, 2009. There was no evidence of under-reporting of SAEs. There were inconsistencies between calculation in the source document vs. the line listing result for remission, for Subject 011 (placebo), Subject 019 (placebo),

Subject 023 (Entocort), from calculated "No" remission at site to line listings having "yes" remission. The FDA field inspector was told that this recalculation was done by the sponsor (See reviewer's note below).

Reviewer note: The CIs were instructed on the eCRFs to calculate the remission rate based on the most severe values for stool frequency and rectal bleeding recorded in the diary in the last 7 days. This was the value calculated at the site. However, according to the Statistical Analysis Plan dated July 15, 2010, the average for stool frequency and rectal bleeding recorded in the diary of the three days closest to the evaluation Visit 5 was to be used. The sponsor was able to re-calculate remission with the three days values after the completion of the trial because the CI site had entered the diary values into the eCRF. As noted above, this recalculation for some subjects at the site resulted in two subjects in the placebo arm and one subject in the comparator arm now being in remission, a re-calculation that is not in favor of the study drug.

A Form FDA 483 was issued for the following violations:

1. Failure to conduct an investigation in accordance with the investigational plan:
   a. Eligibility criteria required that the subjects have a UCDAI score of $\geq$ 4 and $\leq$10. Subject 019 had a UCDAI score of < 4 at screening.
   b. Eligibility criteria required that subjects with laboratory values greater than 2x upper limit of normal be excluded and Subject 022 had a GGT of 111 U/L which was more than twice the upper limit of normal.
   c. A washout period should have occurred immediately after screening completion. The following subjects had washout occur during or following the Visit 2/ Randomization: Subjects #001, 002, 009, and 014.
   d. The protocol required that subjects begin taking the study drug on the day of randomization. The following subjects did not begin taking the drug on the day of randomization: Subjects #001, 002, 003, 006, 014, 018, and 020.
   e. According to the protocol, morning plasma cortisol should be determined between 8-10 AM. For the following subjects, cortisol was taken out side this window on at least one visit: Subject 001 (V1, 3, and 4), Subject 002 (V2), Subject 003 (V1 through 5), Subject 006 (V2 through 5), Subject 007 (V1 through 5), Subject 008 (V1 and 3), Subject 010 (V2 and 3), Subject 011 (V1 and 5), Subject 013 (V1 through 5), Subject 015 (V1 through 3), and Subject 202 (V1).
   f. According to the protocol, subjects were to have oral temperatures recorded at specific visits. The following subjects did not have some oral temperatures recorded: Subject 001 (V1, 3, and 4), Subject 002 (V2), Subject 003 (V1 thru 5), Subject 006 (V2 through 5), Subject 7 (V1 through 5) Subject 008 (V1 and 3), Subject 010 (V2 and 3), Subject 011 (V1 and 5), Subject 013 (V1 thru 5), Subject 015 (V1 thru 3), and Subject 019 (V1).

2. Investigational drug disposition records were not adequate. Specifically, review of 8 of 23 records found that the Subject Investigational Product Inventory Form, where reconciliation of the dispensed treatment kits was recorded, did not match the dosage taken by the subjects as recorded in the subject diaries for Subjects 015 and 020.

3. Failure to maintain adequate and accurate records:
   a. Per the protocol, subjects were to receive their dose of study medication at the clinical site after blood and urine collection. Source records fail to document that subjects received their dosage following blood collection.
   b. Laboratory results for Subject 1 were not on file for Visit 5.

c. **Assessment of data integrity:** (For a discussion of the sponsor's audit report of the clinical investigator site, see Section 3, page 14.) There were numerous GCP violations at this clinical site. This site was noted by the sponsor as one of the sites that should be excluded from the safety and efficacy analysis. OSI's purpose in visiting this site was to examine data integrity, and, the preliminary classification of this inspection is VAI. Based on the FDA inspection of this site, OSI cannot conclude that the GCP violations noted impact primary efficacy outcome or subject safety. However, the sponsor's audit findings at this site were of greater concern – see Section 3, page 16 below for further discussion.

6. **Sponsor/Monitor/CRO: Cosmo Technologies Ltd./Santarus, Inc.**
San Diego, CA

Note: Observations noted for this inspection are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected:** The sponsor proposed that data generated by four sites participating in CB-01 02/02 be excluded from the efficacy analysis. These were Sites 1040 in Italy, Site 1106 in Russia, and Sites 1082 and 1122 in Slovakia. The field investigator reviewed the monitoring reports and plans for the above sites. The field investigator reviewed organization and personnel, financial disclosures, and drug accountability records with special attention to monitoring of the sites in Europe and USA.

b. **General observations/commentary:** The field investigator noted that, at the sites which were excluded by the sponsor, no monitoring deficiencies were observed. The sponsor inspection did not reveal any violations or monitoring problems.

c. **Assessment of Data Integrity:** The sponsor inspection revealed proper monitoring and the data generated by the study can be used in support of the application.

III. REVIEW OF SPONSOR AUDIT REPORTS (By Site):

According to the sponsor submission, at the conclusion of patient enrollment at the 80 activated sites participating in Budesonide Clinical Study CB-01-02/02, For-Cause investigations identified two sites (1106 (Russia) and 1040 (Italy)) that required audits, and the process of Data Validation and External Data Reconciliation (ICON SOP CP05.4) identified five sites (Sites 1082 and 1122 in Slovakia, Site 1111 in Russia, Site 1059 in Poland, and Site 1098 Ukraine) that required audits. The audits for the first two sites (Russia and Italy) were conducted by ICON, the CRO responsible for the monitoring in the study. The audits of the five remaining sites were conducted by an independent auditor.

On May 3, 2012, in response to an information request (IR) from the review division requesting specific details on the GCP violations, the sponsor provided a summary of some of the critical findings. OSI requested the audit reports to provide a better understanding of the nature of the violations and the critical findings. On August 3, 2012, in response to an IR from the Office of Scientific Investigations, the sponsor submitted the audit reports for the seven Protocol CB-01 02/02 sites noted above that were audited.

Reviewer note: The audits appear to have been conducted using the ICH E6 guidelines as a benchmark for GCP assessment. Thus, all aspects of GCP including sponsor quality assurance and quality control, protocol design and investigator brochure, as well as items specific to the clinical investigator, may be cited in an audit of a clinical trial site. Observations were rated as critical, major, minor or other.
Critical: Conditions or practices were noted that adversely affect one or more of the following: product quality; rights, safety or well being of subjects; quality and/or integrity of the data, documentation or other output. Serious non-adherence to ICON procedures/ISO standards is also included in this level. This observation has the potential to result in significant legal and/or regulatory liability to ICON, and represents major non-compliance with ICON policies and/or procedures.
Major: Conditions or practices were noted that represent major deviations from accepted standards and ICON procedures and may adversely affect one or more of the following, <u>if appropriate actions are not implemented effectively:</u> product quality; rights, safety or well being of subject; quality and/or integrity of the data, documentation or other output. This observation has the potential to result in legal and/or regulatory liability to ICON and represents direct noncompliance with ICON policies and/or procedures.
Minor observations are considered “isolated observations that deviate from accepted standards and documented procedures and that, by the isolated observation alone, would not be expected to adversely affect” the rights of subjects or the quality and/or integrity of the data.
Other observations are presented where applicable but do not require a written response.

The following section contains a brief summary of each audit report.

1. Italy Site 1040:

This site had 11 subjects randomized. There were a total of 3 critical findings, 8 major findings, and 16 minor findings. The following are critical findings:

1. The principal investigator did not have adequate oversight of the study conduct or of the sub-investigators who were delegated responsibility in accordance with ICH GCP. The study assessments were conducted by the sub-Investigators who had no interaction with the PI.
2. The sub-Investigator (sub-I) had not received adequate training and supervision in accordance with GCP. This person was not a gastroenterologist and had no training in assessment of the colonoscopy reports or clinical assessment related to the study.
3. There were a number of inconsistencies concerning colonoscopy reports for three subjects and the overall impression is that the reports had not been reviewed before the subjects were enrolled:
   a. The colonoscopy reports filed for baseline appeared to have been printed out after the subjects had been enrolled.
   b. For two subjects, the colonoscopy results indicated that they should have been excluded from the study. The sub-I responsible for performing the colonoscopies had no input into the interpretation of the information for study purposes.
   c. The reports did not include all the required information for the purposes of the Endoscopic Index Assessment (EIA) and Clinical Activity Index (CAI) scoring.
   d. Several inconsistencies between the reports and the information in the eCRFs were noted during the audit (not specified in the report).

   The major findings concerned issues related to poor source documentation, data handling such that items in the source (concomitant medications, adverse events) were not entered into the eCRF, inconsistent completion of subject diaries, use of Asacol making a subject ineligible, monitoring issues, and lack of investigator oversight concerning review of laboratory reports.

To assess data integrity at other sites in Italy, re-monitoring of completed patients was performed at three other Italian sites: 1038, 1043, and 1047. Discrepancies noted at these sites were raised and resolved.

2. Russia Site 1106:

This site had 11 subjects randomized. There were a total of two critical findings, six major findings, and five minor findings. The following are critical findings.

1. The quality of the source data for all reviewed subjects was found to be not adequate as per ICH GCP requirements. There were many corrections and insertions that were in different color pen and were not initialed and dated. There was evidence of use of correction fluid (white-out) and records were not legible.
2. Limited GCP knowledge was demonstrated during the audit review and no GCP training evidence was found in the study team CVs. The sub-I was not able to communicate in English so could not review the subject data entered, in English, into the eCRFs by the data manager.

The major findings included issues related to data accuracy concerning CI review of subject diaries, recording of concomitant medication, site not provided with the updated Patient Diaries, the colonoscopy device used by this site had no valid certificate, the CI did not have adequate oversight of the trial, and the monitoring visit reports did not accurately reflect the level of non-compliance identified during the audit.

To assess the data integrity at other sites in Russian, site assessment visits were performed at Sites 1074, 1115, 1107, and 1112. All data at Site 1114 was re-monitored by independent CRAs

3. Slovakia 1082

This site had six subjects randomized. There were a total of five critical findings, one major finding, and seven minor findings. The following are critical findings.

1. There was no consistent GCP approach to modifications of the protocol. There were changes to the diary and memos to study staff concerning the use of the diary data. There was no plan provided concerning how to implement the changes to subjects who were already participating and whether the changes would be applied retrospectively.
2. The protocol did not state how the parameters of UCDAI, CAI, and EIA should have been assessed or that two of them (UCDAI and CAI) should have been cross linked with diary data. For two subjects, Subjects 1082001 and 1082006, it was not clear who made the EIA assessments
3. There were no written instructions to the CIs regarding how they should instruct the subjects to complete the diaries.
4. Study notes were inadequate. Specifically, it was not accurately documented in the study notes which investigators had seen which subjects for each visit. The investigators confirmed that they cut and pasted notes from different visits. The fax machine at the site did not have toner, so laboratory reports were not legible. Changes were made to the notes without documentation of who made the changes and when. Liquid paper/correction fluid was used on source documents. Duplicate sets of notes had been printed for Subject 1082005 and these had different content.
5. There were a large number of discrepancies between the source and the eCRF data.

The major observation concerned the lack of documentation that the PI had reviewed the laboratory reports at the site. A minor observation was that, in some cases, only partial or "short" colonoscopies were performed at Visit 5 despite the protocol requirement to perform "full" colonoscopies. Subjects 006 and 007 had short colonoscopies for clinical reasons.

4. Slovakia Site 1122

This site had 22 subjects randomized. There were a total of four critical findings, two major findings, and six minor findings. The following are critical findings.

1. There was no consistent GCP approach to modifications of the protocol. There were changes to the diary and memos to study staff concerning the use of the diary data. There was no plan provided concerning how to implement the changes to subjects who were already participating and whether the changes would be applied retrospectively.
2. The protocol did not state how the following parameters should have been assessed or that the UCDAI and the CAI should have been cross linked with diary data.
3. Diary data was not consistently collected and its accuracy in the eCRF could not be confirmed. The subjects sometimes arrived for visits with large sections of the diaries blank

and the CI would assist in filling out the diary. For example, there was confusion concerning whether "normal" stools meant normal for the subject or normally formed. There was confusion concerning how to rate stool frequency. There was confusion because the entry of "0" for stools (normal) would not allow a description of "bloody".

4. It could not be confirmed that the original source data was present for all subjects and there was no audit trail for changes to the source data. For some source data, the notes had been retyped and the old versions destroyed.

The major observation concerned the large number of discrepancies between the source and the eCRF data. This was considered both a site and a monitoring issue. An additional issue concerning monitoring is the PI confusion concerning completion of diaries and whether the AEs recorded in subject diaries should have been reported on the eCRF.
A minor finding was that in some cases only partial or 'short' colonoscopies were performed at visit 5, despite the protocol requirement to perform 'full' colonoscopies. The PI stated that the following subjects had only had the short colonoscopies for clinical reasons: Subjects 0017, 0018 and 10019.

To assess the data integrity of other sites in Slovakia, the sponsor performed the following activities: Site assessments were performed by sponsor personnel (LCRA or PM accompanied by a Slovakian speaker) at all other Slovakian sites: 1081, 1083, 1104, and 1121. In addition, CRAs and LCRAs were trained on the audit findings.

5. Poland Site 1059
This site enrolled 17 subjects. The audit showed no critical findings.

6. Ukraine Site 1098
This site enrolled 17 subjects. The audit showed no critical findings. There was one major finding and one minor finding. The major finding was that appropriate written approval from the regulatory authorities to proceed with the trial was not seen.

7. Russia Site 1111
This site enrolled 22 subjects. The audit showed no critical findings.

Reviewer note: OSI requested submission of these audit reports to determine whether systematic problems in study conduct, such as those identified at four sites by the sponsor preNDA submission, might impact overall study data integrity. Review of the audit reports provides insight into issues concerning study conduct. The Russian and Italian sites had severe GCP violations concerning investigator oversight. For the Slovakian sites, it appears that the observations concerned a lack of adequate source documentation confounded by lack of clarity or specificity in the protocol and poor communication between the sponsor/monitor and the study site. This occurred in areas concerning guidance to the subjects in completing diaries and guidance to the CI concerning determination of which scores to use for determination of eligibility and determination of remission. At those sites that did not understand the instructions from the sponsor and did not receive corrective feedback via monitoring,

numerous GCP violations were noted. From FDA inspection of the additional sites, we see that issues present at the Slovakian site occurred to a lesser extent, either because of better monitoring or better understanding by the investigative site.

Assessment of Data Integrity: Although examination of the above audit reports identified lack of protocol clarity which resulted in some confusion in appropriate calculation of UCDAI scores with variable correction by monitoring, this issue was not identified at all sites audited. In addition, calculation of the primary endpoint at Visit 5 according to the SAP was eventually possible because all the diary data was collected on the CRFs. Therefore, although GCP violations were detected, OSI does not consider that study wide issues impacted overall data integrity for this application. The only inspections for which both a FDA inspection and an audit report are available are for the Bunganic site (Slovakia, Site 1122) and the Petryka site (Poland Site 1059). FDA inspection did not reveal the serious GCP violations noted in the audit report for the Slovakian site. In addition, FDA inspections did not find any violations at the Polish site, and this was in agreement with the audit report. Although the findings at the Bunganic site were not confirmed by our inspection, we agree that the serious GCP violations identified by audit at the Bunganic site merit consideration of exclusion of this site, as proposed by the sponsor.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspection of two sites was originally requested by the review division, but, when it was determined that the sponsor proposed to exclude data from four sites due to GCP violations, inspections were expanded to additional sites to determine whether the violations were more extensive than described by the sponsor. Final classifications of the inspections of the domestic sites, Dr. Chami and Dr Cohen, are NAI and VAI respectively. Final classification of Dr. Petryka's site is NAI and final classifications of the inspections for Drs. Jalihal and Kupcinskas are VAI. The preliminary classifications of the sponsor and Bunganic's site are NAI and VAI respectively. The data generated by Drs. Chami, Cohen, Jalihal, Kupcinskas, and Petryka are considered reliable. Our evaluation of the audit reports did not reveal study wide deficits in study conduct which would have globally impacted data integrity. Although the FDA inspections did not find violations which merited an OAI classification at the Bunganic site, the GCP violations described in the audit report merit consideration for exclusion of this site, as proposed by the sponsor. The data generated by the remaining FDA inspected sites and submitted by the sponsor can be used in support of the indication. Note that the classifications for the inspections of Dr. Bunganic and the sponsor are preliminary, and an addendum to this clinical inspection summary will be written if the conclusions change upon final review.

CONCURRENCE:

{See appended electronic signature page}

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/s/

SUSAN LEIBENHAUT
12/17/2012

SUSAN D THOMPSON
12/17/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 15, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Kevin Bugin, RPM
DGIEP

Subject: QT-IRT Consult to NDA 203634

This memo responds to your consult to us dated March 15 2012 regarding a request to waive a TQT study. The QT-IRT received and reviewed the following materials:

- Your consult
- Investigator Brochure (September 2011)

QT-IRT Comments for DGIEP

We agree that a TQT study is not needed for the following reasons:

- Budesonide (capsules) is being marketed since 1997. The Cmax with the approved formulation ENTOCORT EC is slightly higher than that expected with budesonide MMX (tablets).
- No AEs of concerns as per ICH E14 Guidance have been reported post-marketing.

BACKGROUND

Budesonide is a potent, non-halogenated glucocorticoid structurally related to 16-hydroxyprednisolone. Systemically-sparing corticosteroids such as budesonide are an attractive, alternative treatment option for ulcerative colitis. Budesonide is a moderately potent corticosteroid with low (10% to 15%) systemic bioavailability after oral administration due to extensive first pass hepatic metabolism to metabolites with low anti-inflammatory activity.

Budesonide is approved for treatment of mild to moderate active Crohn's disease since 1997 as ENTOCORT EC. Approved label of ENTOCORT EC, states that the Cmax after 9 mg budenoside is 5 nM.

Budesonide MMX exposure after 6- and 9-mg daily doses

Budesonide Dose	Cmax (pg/mL) (SD)	AUC_{0-t} (pg/mLxh) (SD)
budesonide MMX 6 mg	1158.5 (532.4)	10818.3 (4401.6)
budesonide MMX 9 mg	1348.8 (958.8)	13555.9 (7816.9)

Reviewer's comments: Budesonide MMX systemic exposure after 6- and 9-mg daily dose is > 1 nM (2.5 and 3.1 nM respectively).

SPONSOR'S RATIONALE

From Efficacy Information Amendment, page 7

"Santarus requests a waiver from conducting the Thorough QT (TQT) study, outlined in ICH E14, for the original 505(b)(2) application, NDA 203634 for UCERISTM (budesonide) 9 mg Tablets. The drug substance, budesonide, was originally approved in 1994 under NDA 020233 for Rhinocort® spray. The 505(b)(2) reference drug, NDA 021324 for Entocort EC® Capsules was approved in 2001. Budesonide has a well characterized and safe adverse event profile as demonstrated by the marketed Entocort EC® Capsules. A review of the clinical trials and postmarketing safety information in the current Entocort EC® label does not show any increased risk for causing abnormalities in electrocardiograms (ECGs), including QT prolongation. (Astra Zeneca, 2011). In addition, there is also no evidence for any increased risk of experiencing cardiovascular-related adverse effects with the use of Entocort EC® (Astra Zeneca, 2011). UCERISTM (budesonide) 9 mg Tablets is a minimally absorbed topical steroid product. The low systemic availability of the product reduces the risk of systemic effects. During the clinical development of UCERISTM (budesonide) 9 mg Tablets, three pharmacokinetic (PK) studies were conducted in healthy volunteers. ECGs were recorded from patients during the screening and final visit of the study. The frequency of ECG abnormalities found at screening (sinus arrhythmia, sinus bradycardia, 1st degree atrio-ventricular block, IRBBB, left anterior hemiblock and left ventricle hypertrophy) did not change significantly during the study. ECGs results from the human PK studies can be found in Sequence 0000, CRO-01-28 Section 12.5.1.2, Sequence 0000, CRO-PK-03-105 Section 12.5.1.2, and Sequence 0000, CRO PK-06-178 Section 12.5.1.2.

Santarus has also conducted a literature search with PubMed and BIOSIS using both MESH terms and free texts for “budesonide,” “arrhythmias, cardiac” and “heart function tests” as search terms. This search resulted in no relevant publications regarding any cardiotoxicities associated with the use of budesonide.

“Additionally, during the nonclinical program for UCERISTM a 28 day bridging toxicology and toxicokinetic study was conducted in cynomolgous monkeys. The study compared UCERIS® (budesonide) 9 mg Tablets to the reference drug, Entocort EC® 3 mg capsules. The administration of UCERISTM (budesonide) 9 mg Tablets or Entocort EC® 3 mg capsules for 28 days did not result in any direct or indirect effect on the morphology of the ECG complexes,heart rates, or intervals of the ECG of Cynomolgus monkeys.

“Based on the low systemic availability, human PK data, the well-characterized postmarketing safety profile of Entocort EC®, literature research, and nonclinical data, Santarus requests a waiver from the additional TQT study for UCERIS® (budesonide) 9 mg Tablets.”

QT-IRT Data mining

We conducted an MGPS data mining analysis of the AERS database for AEs related to QT prolongation for budesonide. The signal scores (EBGM value) for all AEs described under “selection criteria” and related to cardiac arrhythmias were lower than 2, suggesting a weak signal similar to the background rate of the general population.

Generic name	PT	HLT	HLGT	SOC	N	EBGM	EB05	EB95
Budesonide	Ventricular arrhythmia	Ventricular arrhythmias and cardiac arrest	Cardiac arrhythmias	Card	3	1.04	0.402	2.30
Budesonide	Syncope	Disturbances in consciousness NEC	Neurological disorders NEC	Nerv	26	0.401	0.288	0.546
Budesonide	Convulsion	Seizures and seizure disorders NEC	Seizures (incl subtypes)	Nerv	46	0.328	0.256	0.415
Budesonide	Ventricular fibrillation	Ventricular arrhythmias and cardiac arrest	Cardiac arrhythmias	Card	2	0.208	0.067	0.523
Budesonide	Electrocardiogram QT prolonged	ECG investigations	Cardiac and vascular investigations (excl enzyme tests)	Inv	3	0.188	0.073	0.416
Budesonide	Ventricular tachycardia	Ventricular arrhythmias and cardiac arrest	Cardiac arrhythmias	Card	2	0.156	0.050	0.393
Budesonide	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	Cardiac arrhythmias	Card	8	0.144	0.079	0.245
Budesonide	Sudden death	Death and sudden death	Fatal outcomes	Genrl	1	0.121	0.028	0.381

Notes	
ID:	7606
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As of date:	05/01/2012 00:00:00
Item variables:	Generic name, PT
Stratification variables:	Standard strata
Highest dimension:	2
Minimum count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base counts on cases:	Yes
Use "all drugs" comparator:	No
Apply Yates correction:	Yes
Stratify PRR and ROR:	No
Fill in hierarchy values:	Yes
Exclude single itemtypes:	Yes
Fit separate distributions:	Yes
Save intermediate files:	No
Created by:	Empirica Signal Administrator
Created on:	05/09/2012 22:14:28 EDT
User:	Monica Fiszman
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 05/01/2012 00:00:00 loaded on 2012-05-09 05:01:42.0
Dimension: 2 Selection Criteria: Generic name(Budesonide) + PT(Cardiac arrest, Convulsion, prolonged, Electrocardiogram QT prolonged, Sudden cardiac death, Sudden death, Syncope, Torsade de pointes, Ventricular arrhythmia, Ventricular asystole, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia)	

Thank you for requesting our input into the development of this product under NDA. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Therapeutic dose	**Include maximum proposed clinical dosing regimen.** Budesonide MMX is given at a fixed dose of 9 mg/day corresponding to a single tablet administered once daily. It is recommended that budesonide MMX be used for a treatment period of up to 8 weeks at a time. Repeat courses for 8 weeks may be given.
Maximum tolerated dose	**Include if studied or NOAEL dose** The maximum tolerated dose for budesonide MMX has not been established in formal clinical trials. The maximum dosage strength tested in the clinical program was 9 mg/day for up to 120 days at a time. Overall, the budesonide MMX 9 mg dosage strength was found to be well-tolerated with a favorable safety profile. As a topically-active corticosteroid with limited systemic bioavailability, a wide therapeutic index is anticipated for budesonide MMX. Additional information regarding other oral budesonide dosage forms in literature can be found in Appendix 1.
Principal adverse events	**Include most common adverse events; dose limiting adverse events** The principal AEs reported in the Phase III placebo-controlled studies (CB-01-02/01 and CB-01-02/02) were colitis ulcerative (worsening of underlying disease), headache, nausea, abdominal pain, diarrhea, flatulence and nasophyaryngitis. Two dosage strengths for budesonide MMX (6 mg/day and 9 mg/day) were tested in a placebo controlled design. Adverse event rates were similar in both actively treated patients and placebo subjects Rates for the above AEs in the 9 mg population were 13%, 11%, 5%, 4%, 1%, 2%, and 2% respectively. A Table showing the data for all treatment groups is provided in Appendix 2. Other adverse events occurred at rates below 2% (AEs from the Cardiac Disorders System Organ Class (SOC) affected 3 subjects (1.2%) in each of the groups (Placebo: 2 patients with tachycardia; 1 with palpitations; budesonide MMX 9 mg: 2 patients with palpitations; 1 patient with angina pectoris; budesonide MMX 6 mg: 2 patients with tachycardia; 1 patient with bradycardia). (Sequence 0000, ISS Table 1.10.1)

<table>
<tr><td rowspan="2">Maximum dose tested</td><td>Single Dose</td><td>Specify dose

Budesonide MMX 9 mg</td></tr>
<tr><td>Multiple Dose</td><td>Specify dosing interval and duration

Budesonide MMX 9 mg/day for up to 120 days

Budesonide MMX 6 mg/day for 450 days</td></tr>
<tr><td rowspan="2">Exposures Achieved at Maximum Tested Dose</td><td>Single Dose</td><td>Mean ± SD (%CV) Cmax and AUC
Cmax = 1348.8 ± 958.8 pg/mL (71.1%)
AUC = 16431.2 ± 10519.8 pg hr/mL (64.0%)
(Sequence 0000, CB-01-02/03 CSR)</td></tr>
<tr><td>Multiple Dose</td><td>Mean ± SD (%CV) Cmax and AUC
Cmax = 891.3 ± 394.1 pg/mL (at steady state)
AUC = 9295.2 ± 3694.2 pg h/mL (at steady state)
(Sequence 0000, BUD 1001 CSR)</td></tr>
<tr><td>Range of linear PK</td><td colspan="2">Specify dosing regimen
Budesonide MMX pharmacokinetic for at 6 mg and 9 mg daily doses and results are provided in the table below.
<table>
<tr><th>Budesonide Dose</th><th>Cmax (pg/mL) (SD)</th><th>AUC_{0-t} (pg/mLxh) (SD)</th></tr>
<tr><td>budesonide MMX 6 mg</td><td>1158.5
(532.4)</td><td>10818.3
(4401.6)</td></tr>
<tr><td>budesonide MMX 9 mg</td><td>1348.8
(958.8)</td><td>13555.9
(7816.9)</td></tr>
</table>
Inspection of these data show acceptable proportionality of both Cmax and AUC with dose.

Edsbacker et al also report on the pharmacokinetics of a controlled ileal release product at different doses evaluated in a crossover study and show a similar outcome (variable systemic pharmokinetics and approximately proportional change in AUC and Cmax with dose). (Sequence 0000, Edsbacker, 1999) See Appendix 3.</td></tr>
</table>

Accumulation at steady state	**Mean (%CV); specify dosing regimen** Judged by a comparison of the Day 1 and Day 7 AUC data and other pharmacokinetic parameters for budesonide MMX, there is no accumulation at steady state (Sequence 0000, Brunner, 2005; Sequence 0000 BUD 1001 CSR) The dosing regimen consisted of 7 consecutive days of oral budesonide MMX 9 mg given once daily in the morning to healthy subjects after a standardized meal. The coefficient of accumulation after repeated administration was calculated as the repeated/single dose ratios for Cmax and AUC (Sequence 0000, Table 14.2.9 of BUD 1001 CSR). Mean Cssmax/Cmax was 0.87 ± 0.51 (0.16 –1.57), while the ratio AUCss/AUC∞ was 0.82 ± 0.47 (0.16–1.66). (Sequence 0000 BUD 1001 CSR)	
Metabolites	**Include listing of all metabolites and activity** Following absorption, budesonide is subject to high first pass metabolism (80-90%). *In vitro* experiments in human liver microsomes demonstrate that budesonide is rapidly and extensively biotransformed, mainly by CYP3A4, to its 2 major metabolites: 6β-hydroxy budesonide 16α-hydroxy prednisolone The glucocorticoid activity of these metabolites is negligible (less than 1/100) in relation to that of the parent compound. This was assessed in the rat ear edema test. (Sequence 0009, Entocort EC label 2011, Section 12.3) Santarus has also conducted a literature search with PubMed and BIOSIS using both MESH terms and free texts for "budesonide," "metabolism," "6β-hydroxy budesonide," and "16α-hydroxy prednisolone" as search terms. This search resulted in no relevant publications.	
Absorption	Absolute/Relative Bioavailability	**Mean (%CV)** Budesonide is subject to extensive first pass metabolism; the absolute bioavailability is estimated to be 10-15% (Sequence 0000, Brunner, 2006).
	Tmax	**Median (range) for parent** Median ± SD: 13.3 ± 5.9 hours (9 mg dose) (Sequence 0000, CB-01-02/03 CSR) **Median (range) for metabolites** Not available

Distribution	Vd/F or Vd	**Mean (%CV)** The mean volume of distribution (Vss) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients taking oral controlled ileal release budesonide. (Sequence 0009, Entocort EC label 2011, Section 12.3)
	% bound	85-90% plasma protein bound (Sequence 0009, Entocort EC label 2011, Section 12.3)
Elimination	Route	**Primary route; percent dose eliminated** Prior to excretion, (urine and feces) budesonide is extensively metabolized. After PO or IV administration, [^{3}H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxy budesonide and 16αhydroxy prednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine. (Sequence 0009, Entocort EC label 2011, Section 12.3) **Other routes** Not Applicable
	Terminal t½	**Mean ± SD (%CV) for parent** The mean ± SD (%CV) of the terminal half life of budesonide MMX is: 8.2 ± 3.7 (44.7) (Sequence 0000, CB-01-02/03 CSR) The plasma elimination half-life, $t_{1/2}$, after administration of intravenous budesonide doses ranges between 2 and 3.6 hours. (Sequence 0009, Entocort EC label 2011, Section 12.3)
	CL/F or CL	**Mean** *In vivo* investigations with intravenous doses in healthy subjects are in agreement with the in vitro findings and demonstrate that budesonide has a high plasma clearance, 0.9 –1.8 L/min. (Sequence 0009, Entocort EC label 2011, Section 12.3)

Intrinsic Factors	Age	**Specify mean changes in Cmax and AUC** Not studied
	Sex	**Specify mean changes in Cmax and AUC** No significant pharmacokinetic differences have been identified due to sex. (Entocort EC label 2011, Section 12.3)
	Race	**Specify mean changes in Cmax and AUC** Not studied
	Hepatic & Renal Impairment	**Specify mean changes in Cmax and AUC** Hepatic Insufficiency: In patients with liver cirrhosis, systemic availability of orally administered budesonide increases with disease severity and is, on average, 2.5-fold higher compared with healthy controls. Patients with mild liver disease are minimally affected. Patients with severe liver dysfunction were not studied. Absorption parameters are not altered, and for the intravenous dose, no significant differences in CL or Vss are observed. Renal Insufficiency: The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Some accumulation of the hydroxy-metabolites (which are subject to renal excretion) may occur. These metabolites have negligible (<1%) corticosteroid activity as compared with budesonide. (Sequence 0009, Entocort EC label 2011, Section 12.3)

Extrinsic Factors	Drug interactions	**Include listing of studied DDI studies with mean changes in Cmax and AUC** Potent inhibitors of CYP3A4 can increase the plasma levels of budesonide several fold. Co-administration of ketoconazole results in an eight-fold increase in AUC of budesonide. Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels. (Sequence 0009, Entocort EC label 2011, Section 12.3) A listing of published DDI studies with budesonide is provided in Appendix 4.
	Food Effects	**Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)** Cmax and AUC are reduced in the fed condition following a high-fat meal (by 27% and 6% respectively) (Sequence 0000, BUD 1001 CSR)
Expected High Clinical Exposure Scenario	**Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.** The MMX formulation was designed to deliver drug to the colon as a single oral tablet given once daily. Thus, accidental overdosage from dosing errors is unlikely. The most likely scenario where overdosage could occur, is in the setting of administration with a concomitant CYP inhibitor. Concomitant administration of CYP inhibitors (for example ketoconazole) has been shown to cause increases systemic budesonide concentration although the effect of ketoconazole may be partly due to P-glycoprotein (PGP) inhibition since budesonide is also a substrate for the latter. The hydroxyl metabolites may also be increased if renal function is reduced. (Sequence 0009, Entocort EC label 2011, Section 12.3)	

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/s/

MONICA L FISZMAN
05/15/2012

NITIN MEHROTRA
05/15/2012

NORMAN L STOCKBRIDGE
05/15/2012

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 and Labeling Review

Date:	April 10, 2012
Reviewer:	Anne Crandall Tobenkin, PharmD. Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Names and Strength:	Uceris (Budesonide) Tablets, 9 mg
Application Type/Number	NDA 203634
Applicant	Santarus, Inc.
OSE RCM #:	2012-70

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

1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Uceris (Budesonide) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis evaluated the proposed proprietary name, Uceris, in OSE review # 2011-1390 during the IND phase. Subsequently the application converted to an NDA and the Applicant submitted the labels and labeling for approval during the NDA cycle.

1.2 PRODUCT INFORMATION

- Active Ingredient: Budesonide
- Indication of Use: induction of remission in patients with active, moderate ulcerative colitis
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 9 mg
- Dose and Frequency of administration: One tablet once daily
- How Supplied: Bottles of 30
- Storage: Room temperature
- Container and Closure Systems: (b) (4) child-resistant safety cap

2 METHODS AND MATERIALS REVIEWED

Using the principles of Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 14, 2011
- Insert Labeling submitted December 14, 2011

Additionally, since this proposed product is similar to Entocort EC, a currently marketed Budesonide product, which has the same indication, dose, and frequency, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Entocort EC. The February 9, 2012 AERS search was conducted using the following search terms: active ingredient (Budesonide) and trade

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

name (Entocort) and HLGT terms (Medication Errors and Product Quality Issues). No time limit was set for the search.

All reports were screened for medication errors. Cases that did not involve medication errors were excluded from further analysis. Reports describing a medication error were screened for duplicates. All duplicates were combined into cases and further categorized by type of error. These cases were evaluated for all contributing factors to the error.

All of the cases identified in the search were not relevant to the review for the following reasons: the cases involved intentional overdose of a product unrelated to Uceris, issues related to the capsule (Uceris will be tablet form as opposed to Entocort EC which is a capsule), lack of effect, adverse events associated with the use of Entocort EC, and missed or skipped doses due to financial hardship.

3 CONCLUSIONS AND RECOMMENDATIONS

We concur with the introduction of the proposed 9 mg strength of Budesonide because it allows for a one tablet dose and aligns with the current prescribing of Budesonide for the indication of active, mild to moderate ulcerative colitis. Review of the submitted labels identified that the strength statement lacks prominence and should be relocated and the frequency statement should be removed from the principal display panel. We advise the following recommendations be implemented prior to approval of this NDA:

A. Container Label

1. Relocate the '9 mg' strength statement so that it appears after the 'tablet' dosage form statement.
2. Box the strength statement, '9 mg' and increase the font size, in order to highlight the strength difference between Uceris and other currently marketed Budesonide products.
3. Relocate the 'once daily' frequency of administration statement from the principal display panel to the back panel. Communicating the frequency of administration on the principal display panel is reserved for circumstances in which the proposed product differs from the current standard, which is not the case for the proposed Budesonide product. Additionally, revise the statement so that it reads, 'Usual dose: one tablet once daily, see insert for instructions'.
4. Remove the 'budesonide, 9 mg' statement on the back of the container label as it is redundant and contributes to clutter.

If you have further questions or need clarifications, please contact Nitin Patel, OSE Project Manager, at 301-796-5412.

APPENDIX

Appendix A: Proposed Container Labels (submitted December 15, 2011)

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/s/

ANNE C TOBENKIN
04/10/2012

LUBNA A MERCHANT
04/10/2012

CAROL A HOLQUIST
04/10/2012

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

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

Application: NDA 203634

Name of Drug: Uceris (budesonide) 9 mg

Applicant: Santarus, Inc

Labeling Reviewed

Submission Date: 12/14/2012

Receipt Date: 12/16/2012

Background and Summary Description

Budesonide MMX 9 mg tablets is an enteric coated, extended release, oral dosage formulation designed for the induction of remission in adult patients with active, mild to moderate ulcerative colitis (UC). UC is a chronic, relapsing/remitting inflammatory bowel disease (IBD) involving the colorectal mucosa. According to the sponsor, to provide an enhanced standard of treatment for UC, budesonide, a topically-active glucocorticosteroid, was selected as the active ingredient and combined with the novel, patented multimatrix (MMX) delivery technology.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by March 20, 2012. The resubmitted labeling will be used for further labeling discussions.

Kevin Bugin	02/28/2012
Regulatory Project Manager	Date
Wes Isihihara	02/28/2012
Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☒ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)

- **Revision Date** (required information)

- **Highlights Limitation Statement**

  ☒ Must be placed at the beginning of HL, **bolded,** and read as follows: "**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).**"

- **Product Title**

  ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

  ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning.***" If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

  ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) -- 2/2010."

  ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.

  ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) ~~ removal 2/2010."

- **Indications and Usage**

☒ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

☐ All contraindications listed in the FPI must also be listed in HL.

☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

☒ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**

☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection 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."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for

the text.

☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

  ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

  ☐ For the "Clinical Trials Experience" subsection, 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."

  ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

  > "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."

- **Use in Specific Populations**

  ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

  ☐ This section is required and cannot be omitted.

  ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

  - "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)"

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/s/

KEVIN B BUGIN
02/27/2012

RICHARD W ISHIHARA
02/27/2012

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 # 203634 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Uceris Established/Proper Name: budesonide Dosage Form: Tablet Strengths: 9 mg		
Applicant: Santarus, Inc Agent for Applicant (if applicable):		
Date of Application: 12/15/2012 Date of Receipt: 12/16/2012 Date clock started after UN:		
PDUFA Goal Date: 10/16/2012	Action Goal Date (if different):	
Filing Date: 02/14/2012	Date of Filing Meeting: 01/25/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): Induction of remission in patients with mild to moderate ulcerative colitis		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 074882	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	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)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***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.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
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)].**		X		
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)]?** ***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 (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***		X		Different indications.
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 Years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
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:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	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 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

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]. ***Note:*** *Debarment Certification should use wording in FDCA 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…"*				
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

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

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Full waiver submitted.

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

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? ***If no, request in 74-day letter***			X	
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)? ***If no, request in 74-day letter***	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
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) ***If yes, specify consult(s) and date(s) sent:***	X			QT Study Report, OSI
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		See 1.6.3 in eCTD

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Type B PreNDA Meeting Minutes – 07Jun11 ***If yes, distribute minutes before filing meeting***	X			See 1.6.3 in eCTD
Any Special Protocol Assessments (SPAs)? **Date(s):** Type A SPA Meeting Minutes – 27Mar08 – No agreement reached. ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			See 1.6.3 in eCTD

ATTACHMENT

MEMO OF FILING MEETING

DATE: 01/25/2012

BLA/NDA/Supp #: 203634

PROPRIETARY NAME: Uceris

ESTABLISHED/PROPER NAME: budesonide

DOSAGE FORM/STRENGTH: 9 mg tablet

APPLICANT: Santarus, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):
Induction of remission in patients with active mild to moderate ulcerative colitis.

BACKGROUND: Budesonide 9 mg tablets is an enteric coated, extended release, oral dosage formulation designed for the induction of remission in adult patients with active, mild to moderate ulcerative colitis (UC). UC is a chronic, relapsing/remitting inflammatory bowel disease (IBD) involving the colorectal mucosa. According to the sponsor, to provide an enhanced standard of treatment for UC, budesonide, a topically-active glucocorticosteroid, was selected as the active ingredient and combined with the novel, patented multimatrix (MMX) delivery technology.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kevin Bugin	Y
	CPMS/TL:	Wes Ishihara	Y
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		Y
Clinical	Reviewer:	Marjorie Dannis	Y
	TL:	Anil Rajpal	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Dilara Jappa	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Milton Fan	Y
	TL:	Mike Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dinesh Gautam	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ray Frankewich	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Li Zhong	N
	TL:	Lori Gorski	Y
OSE/DMEPA (proprietary name)	Reviewer:	Ann Tobenkin	N
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Khairy Malek	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**: Waiver of PREA requirements submitted, but not acceptable.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: Not a new molecular entity. ***If no, for an original NME or BLA application, include the reason. For example:***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Need PK analyses datasets	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: CE not applicable, Sponsor has been informed to resubmit appropriate CE.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Donna Griebel/Andrew Mulberg

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.

☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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 DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	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 at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Kevin Bugin	See electronic signature.
Regulatory Project Manager	Date
Wes Ishihara	See electronic signature.
Chief, Project Management Staff	Date

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/

KEVIN B BUGIN
02/27/2012

RICHARD W ISHIHARA
02/27/2012