CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203634Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203634 SUPPL # HFD # 180

Trade Name Uceris

Generic Name budesonide

Applicant Name Santarus, Inc

Approval Date, If Known 16 Jan 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	020746	Rhinocort
NDA#	021929	Symbicort
NDA#	020441	Pulmicort
NDA#	021949	Pulmicort Flexhaler
NDA#	020929	Pulmicort Respules
NDA#	21324	Entocort EC

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer

to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

CB-01-02/01
CB-01-02/02
CB-01-02/06

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

Investigation #3 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation

and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

CB-01-02/01
CB-01-02/02
CB-01-02/06

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!	
	!	
IND # 74882	YES ☒ !	NO ☐

! Explain:

Investigation #2 !
!
IND # 74882 YES ☒ ! NO ☐
! Explain:

Investigation #3 !
!
IND # 74882 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Kevin Bugin
Title: RPM
Date: 10 Jan 2013

Name of Office/Division Director signing form: Andrew E Mulberg
Title: Deputy, DGIEP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

ANDREW E MULBERG
01/10/2013

From: Bugin, Kevin
To: Matthew Moran (MMoran@santarus.com)
Cc: Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject: NDA 203634 Uceris (budesonide MMX) - Clinical Request for Information - February 13, 2012
Date: Monday, February 13, 2012 11:57:41 AM
Attachments: image003.png

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical sections of your submission and have the following comments and information requests. We request prompt written response in order to continue evaluation of your NDA.

1. Provide a summary exposure table showing the numbers of subjects that received budesonide MMX by cohorts based on duration of dosing (across all clinical studies of budesonide MMX); the table should provide overall exposure data (pooled across all studies) and exposure data by population (i.e., ulcerative colitis patients, and healthy volunteers). Exposure data should be summarized by dose (i.e., 3 mg QD, 6 mg QD, and 9 mg QD). The table should look substantially like the following:

All Clinical Studies of budesonide MMX										
	Duration of Dosing									
	≥ 1 dose	≥ 1 wk	≥ 2 wks	≥ 1 mo.	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	≥ 15 mo.	≥ 18 mo.	≥ 24 mo.
Overall										
9 mg QD	n	n	n	n	n	n	n	n	n	n
6 mg QD	n	n	n	n	n	n	n	n	n	n
3 mg QD	n	n	n	n	n	n	n	n	n	n
Ulcerative Colitis										
9 mg QD	n	n	n	n	n	n	n	n	n	n
6 mg QD	n	n	n	n	n	n	n	n	n	n
3 mg QD	n	n	n	n	n	n	n	n	n	n
Healthy volunteers										
9 mg QD	n	n	n	n	n	n	n	n	n	n
6 mg QD	n	n	n	n	n	n	n	n	n	n
3 mg QD	n	n	n	n	n	n	n	n	n	n

2. Provide the adverse event "coding dictionary" consisting of a list of all investigator verbatim terms and the preferred terms to which they were mapped. Please submit this as a SAS transport file.

3. Provide a data listing of all serious adverse events and other events that resulted in dropouts across all your studies (by subject identification number). Include the study number, treatment group, and links to the corresponding narrative summaries.

4. Provide a brief summary discussion (limited to a few pages) about the benefits and risks of your product.

5. Provide a brief discussion (limited to a few pages) about your rationale for the applicability of foreign clinical data in your application to the U.S. population and practice of medicine.

6. You have not submitted a Thorough QT (TQT) study as part of your NDA for Uceris (budesonide MMX). If you do not perform a TQT study, you will need to submit a formal request for a waiver of the requirement for a TQT study with adequate justification (based in part on human PK data) for FDA to review (see ICH E14). Submit your request for a waiver as soon as possible.

7. We do not agree with the rationale you have provided for a request for a [redacted] (b) (4) (see Section 1.9.1 of your submission). We generally have waived requirements for pediatric studies of UC treatment for the age subpopulation

below 5 years because of the low incidence of UC in that subpopulation, and granted a deferral for studies in the age subpopulation of 5 years and above. We recommend that you submit a partial waiver request for ages 0 to 4 years, and a deferral request for ages 5 to 17 years. You should also submit a Pediatric Plan that outlines pediatric studies that you plan to conduct; the Pediatric Plan should also address the development of an age-appropriate formulation. (See the Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, September 2005.)

8. For each of the Phase 3 studies (Study CB-01-02/01 and CB-01-02/02), provide the following subgroup analyses for the primary efficacy endpoint:
   a. Age (<65 vs. ≥65)
   b. Race
   c. Smoking status (ex-smoker vs. smoker vs. non-smoker)
   d. Country
   e. Baseline UCDAI score (4 vs. 5 vs. 6 vs. 7 vs. 8 vs. 9 vs. 10)
   f. Baseline CRP (<10 mg/L vs. ≥10 mg/L)
   g. Concomitant medication use status
      [categories of concomitant medication use: (1) concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) vs. (2) concomitant non-topical corticosteroids vs. (3) concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) and/or concomitant non-topical steroids vs. (4) neither concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) nor concomitant non-topical steroids]

9. For each of the Phase 3 studies (Study CB-01-02/01 and CB-01-02/02), perform a statistical analysis for treatment group comparability at baseline for demographic and baseline characteristics.

10. Perform a "true" ITT analysis for the primary efficacy endpoint in each of the Phase 3 studies (Study CB-01-02/01 and CB-01-02/02). The "true" ITT analysis should include all subjects that were randomized.

11. Please perform the following sensitivity analyses for the primary efficacy endpoint in each of the Phase 3 studies (Study CB-01-02/01 and CB-01-02/02):
    a. Complete case: exclude subjects from the analysis at all time points if they have insufficient data at any of the time points of analysis.
    b. Observed case: exclude patients from the analysis at a specific time point if the patient has insufficient data at that time point.
    c. Worst case (1): subjects with missing observations at any of the time points of analysis are assumed to have "failed";
    d. Worst case (2): subjects receiving placebo with missing observations at any of the time points of analysis are assumed to be responders, and subjects receiving treatment with missing observations at any of the time points of analysis are assumed to be non-responders.
    e. LOCF analysis
    f. Multiple imputation

We request that you respond to these requests for information or provide us with an estimated submission timeframe by March 02, 2012. If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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
02/13/2012

1.3.3 DEBARMENT CERTIFICATION

Santarus, Inc. 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 new drug application 203634 for Uceris (budesonide) 9 mg Tablets.

Maria Bedoya-Toro, Ph.D., M.B.A.
Senior Vice President, Regulatory Affairs and Quality Assurance

11/29/11
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203634 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Uceris Established/Proper Name: budesonide Dosage Form: 9 mg tablets		Applicant: Santarus, Inc Agent for Applicant (if applicable):
RPM: Kevin Bugin		Division: DGIEP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Entocort EC (NDA # 21324)

Provide a brief explanation of how this product is different from the listed drug.

This product is for a new indication. It is also a new formulation.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 14 Jan 2013

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 16 Jan 2013 (Action on 14 Jan 2013)	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 3

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No

CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist[4]	14 Jan 2013
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 01/16/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	01/10/2013
• Original applicant-proposed labeling	12/16/2011
• Example of class labeling, if applicable	Entocort EC – Dec 2011

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	01/10/2013
• Original applicant-proposed labeling	12/16/2011
• Example of class labeling, if applicable	Entocort EC – Dec 2011
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	19 Dec 2012
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	04/17/2012 12/11/2012; 07/25/2012;
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 02/27/2012 ☒ DMEPA 04/10/2012 ☒ DMPP/PLT (DRISK) 12/26/2012; 12/21/2012; ☒ ODPD (DDMAC) 12/28/2012; 12/20/2012 ☒ SEALD 01/02/2013 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	02/27/2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 01/03/2013
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 01/10/2013
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 11/28/2012 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable; 01/10/2013;
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	01/10/2013; 01/10/2013; 01/03/2013; 12/31/2013; 12/19/2012; 12/14/2012; 08/08/2012; 08/01/2012; 07/24/2012; 07/20/2012; 06/13/2012; 06/11/2012; 05/31/2012; 05/23/2012; 05/16/2012; 04/30/2012; 04/23/2012; 03/01/2012; 02/28/2012; 02/13/2012; 01/30/2012; 01/30/2012; 01/24/2012; 01/23/2012; 12/27/2012;
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 05/31/2011
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	SPA Meeting 03/07/2008
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 01/14/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 01/14/2013
PMR/PMC Development Templates *(indicate total number)*	☐ None 01/11/2013
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL
• Clinical review(s) *(indicate date for each review)*	12/12/2012; 02/06/2012
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review, Section 3.3, Page 10

[6] Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 12/21/2012; 12/21/2012; 12/21/2012; 12/17/2012;
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 12/31/2012
Statistical Review(s) *(indicate date for each review)*	☐ None 12/21/2012; 01/27/2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/19/2012; 02/10/2012
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/15/2012; 01/18/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 01/14/2013; 11/09/2012; 02/14/2012 Biopharm 12/12/2012; 01/31/2012
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Section II.B (CMC Assessment) of CMC Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: See CMC Review Dated 01/14/2013 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE's ADRA.

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Container Label Revisions - January 10, 2013
Date:	Thursday, January 10, 2013 3:33:53 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide).

Also, refer to the Container Label submitted on December 19, 2012. We have the following requests for revisions to the container labeling.

1) Remove the (inner and outer) circular graphics from the principal display panel as they are distracting and decrease the prominence of drug identifying information;

2) Revise the established name so that it is at least 1/2 (half) the size of the proprietary name and has prominence commensurate to that of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

3) Relocate the statement of strength to appear below the established name (e.g., active ingredient and dosage form).

4) Debold the statement on the side panel, (b) (4) .

5) Decrease the prominence of the Santarus logo on the side panel as it competes with more important information.

6) Revise the usual dosage statement to read "Usual dose: one tablet daily, see full prescribing information. Delete the statement "(b) (4)" as this is redundant to the usual dosage statement.

7) Relocate the statement "Uceris should be swallowed whole and not chewed or broken" (on the side panel) to appear just below the "Usual dose" statement to consolidate dosage and administration information.

8) Add the statement "Swallow tablet whole, do not chew or break" to the principal display panel.

9) Decrease the prominence of the net quantity and Rx only statements so that they do not compete with the prominence of drug identifying information.

10) Delete the "patent numbers" (U.S. Patent Nos . .) from the side panel as they clutter the label and this information can be in the insert labeling.

11) Temperature requirement listed on the side panel should say “Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F)”

If you have any questions, please let me know.

Regards,

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
01/10/2013

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Labeling and Post Marketing Comments - January 10, 2013
Date:	Thursday, January 10, 2013 11:05:23 AM
Attachments:	CLEAN NDA 203634 Uceris (budesonide) -FDA Labeling Revisions 10Jan2013.doc REDLINED NDA 203634 Uceris (budesonide) - FDA Labeling Revisions 10Jan2013.pdf

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide).

Attached please find an MS Word document which contains FDA's final labeling proposal. The MS Word document is a clean version with a few comments for your attention. To facilitate your review, I have also included a redlined PDF. I would normally include a redlined Word document but it appears during the revision process something bloated the MS file and created some errors which made this difficult.

Also, below please find the revised language and milestones for the PREA required post marketing requirement (PMR) that you will be responsible for. We have considered your counter proposal.

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

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

Please let me know if you have any questions, or if you believe you would require discussion on either the labeling or the PREA PMR.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
01/10/2013

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Post Marketing Comments - January 3, 2012
Date:	Thursday, January 03, 2013 2:12:45 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide).

Below please find the language for the PREA required post marketing requirement (PMR) that you will be responsible.

> An 8-week randomized, double-blind, placebo-controlled trial to evaluate pharmacokinetics (PK), efficacy for induction of remission, and safety of Uceris (budesonide) in children 5 to 17 years of age with active, mild to moderate ulcerative colitis. At least 2 doses of Uceris (budesonide) will be evaluated. The effects of 8 weeks of Uceris (budesonide) on the HPA axis will be assessed.
>
> | | |
> |---|---|
> | Final Protocol Submission: | 06/2013 |
> | Trial Completion: | 06/2015 |
> | Final Report Submission: | 12/2015 |

Please let me know if you have any questions.

Regards,

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
01/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203634

ACKNOWLEDGE CORPORATE NAME/ADDRESS CHANGE

Santarus, Inc
Attention: Matthew E. Moran, M.S.,
Senior Director, Regulatory Affairs
3611 Valley Centre Drive, Suite 400
San Diego, CA 92130

Dear Mr. Moran:

We acknowledge receipt on December 20, 2012, of your correspondence notifying the Food and Drug Administration (FDA) that the corporate address has been changed from

3721 Valley Centre Drive, Suite 400
San Diego, CA 92130

to

3611 Valley Centre Drive, Suite 400
San Diego, CA 92130

for the following new drug application (NDA):

NDA 203634 for UCERIS (budesonide).

We have revised our records to reflect this change.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN
12/31/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Labeling Comments - December 19, 2012
Date:	Wednesday, December 19, 2012 5:38:19 PM
Attachments:	Clean_NDA 203634 Uceris (budesonide) - FDA Labeling Revisions - December....doc Redlined_NDA 203634 Uceris (budesonide) - FDA Labeling Revisions - Decem....doc

---

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide).

Please find attached two WORD documents containing FDA's revisions to the proposed labeling. The October 18, 2012, version of labeling was used as the base for these revisions. One version is clean and one contains revisions tracked for ease of review.

If you have any questions, please let me know.

Regards,

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
12/19/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - DMEPA Carton and Container Labeling Comments - December 14, 2012
Date:	Friday, December 14, 2012 1:53:09 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

The Division of Medication Error Prevention and Analysis (DMEPA) has concluded its initial review of your carton and container labeling, and have the following comments and requests for revisions.

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 '(b) (4)' statement on the back of the container label as it is redundant and contributes to clutter.
5. Add "Uceris should be swallowed whole and not chewed or broken" to the carton and container labeling.

If you have any questions, please do not hesitate to contact me.

Regards,

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
12/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203634

REVIEW EXTENSION – MAJOR AMENDMENT

Santarus, Inc.
Attention: Maria Bedoya-Toro, Ph.D., M.B.A.
Vice President, Regulatory Affairs and Quality Assurance
3721 Valley Centre Drive, Ste. 400
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) dated December 14, 2012, received December 16, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Uceris (budesonide) 9 mg tablets.

On August 03, 2012, we received your solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 16, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 12, 2012.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Andrew Mulberg, MD, FAAP, CPI
Deputy
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
08/08/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Clinical Pharmacology Request for Information - August 01, 2012
Date:	Wednesday, August 01, 2012 10:05:21 AM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical pharmacology sections of your NDA and have the following comments and requests for information. We request prompt written response in order to continue evaluation of your NDA.

- Regarding Study CB-01-02/04, please submit the individual ACTH (Synacthen test) results including cortisol level at pre-dose, post-dose and difference between post-dose and pre-dose for each individual. Please indicate the percentage of patients who had normal ACTH stimulation test for both the treatment and placebo arms according to the criteria for a normal ACTH response as specified in the Synacthen label.

If you have any questions, please do not hesitate to contact me.

Kind regards,

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
08/01/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Clinical Pharmacology Request for Information - July 24, 2012
Date:	Tuesday, July 24, 2012 9:03:07 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical pharmacology sections of your NDA and have the following comments and requests for information. We request prompt written response in order to continue evaluation of your NDA.

1. We have the following comments and requests for clarification for Study CRO-PK-03-105:
    a. Explain the difference in single dose PK profiles under fasting conditions in Figures 11.4.1 and 11.4.3. We note that these profiles are supposed to be based on the same data.
    b. Clarify how AUC_{ss} was estimated (i.e., what the time interval is in the AUC_{ss} calculation).
    c. For a multiple dose study, you should report $AUC_{0\text{-}tau}$. You should use $AUC_{0\text{-}24}$ after single dose and multiple dose administration to estimate the accumulation ratio.
    d. Clarify the meal time relative to the dosing time on the PK sampling days in the multiple dose study.

2. We have the following requests for clarification for Study CRO-01-28:
    a. Clarify how AUC_{colon} was estimated.
    b. Clarify how disintegration time was defined.
    c. Clarify how the location of the radioactivity in the GI gut was determined.

3. For Study CRO-PK-06-178, clarify if you used compartmental or non-compartmental analysis to determine the PK parameters.

4. Please conduct a literature search to address the following:
    a. If budesonide is inhibitor/inducer of CYP enzymes.
    b. If budesonide is a substrate/inhibitor of transporter(s).

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products

CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
07/24/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Office of Compliance Request for Information - July 20, 2012
Date:	Friday, July 20, 2012 3:56:07 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We request prompt written response in order to continue evaluation of your NDA.

1. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
   e. The monitoring plans for each of the clinical trials, including all versions of the plans, dates and nature of the revisions.

2. Please provide monitoring reports and audit reports for the following sites that participated in Budesonide Clinical Study CB-01-02/02: 1106, 1040, 1082, 1122, 1111, 1059, and 1098.

3. Please provide a copy of ICON SOP CP05.4 (Data Validation and External Data Reconciliation).

4. We understand that you provided a CD in triplicate to Joseph Peacock at the request of Dr. Khairy Malek. Please submit the information contained on the CD to the NDA.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave

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KEVIN B BUGIN
07/20/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Clinical Request for Information - June 13, 2012
Date:	Wednesday, June 13, 2012 11:20:36 AM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical sections of your submission and have the following comments and information requests. We request prompt written response in order to continue evaluation of your NDA.

- You have not provided remission status in the specific datasets that were submitted on May 3 (see page 11/14). Please add the remission status column to those specific datasets and resubmit as sas transport files (.xpt).

If you have any questions, do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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/s/

KEVIN B BUGIN
06/13/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide) - Clinical Pharmacology Request for Information - June 11, 2012
Date:	Monday, June 11, 2012 11:43:06 AM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical pharmacology sections of your submission and have the following comments and information requests. We request prompt written response in order to continue evaluation of your NDA.

> We note that in your phase 2 (CRO -3-53) and phase 3 (CB-01-02/04) studies, you have used Synacthen test which uses stimulation with tetracosactide (0.25 mg given as im) for ACTH test to assess HPA axis suppression. Currently in the United States, cosyntropin is approved as a diagnostic for assessing HPA axis suppression (0.25 mg given as iv). Please clarify what are the differences between these two products.
>
> Additionally, the criteria for normal response to exclude HPA axis impairment in your study ("Clinical criteria of interpretation of the test findings are that the cortisolemia should be normal at pre-dose, i.e. it should fall in the interval 7.25-21.75 µg/dL. After adrenocorticotropic stimulation cortisolemia should be ≥15.95 µg/dL and the increment should be of at least 6.16 µg/dL in order to exclude an axis impairment" on page 64 of Study report CRO-03-53) appears to be different from the criteria in Cosyntropin label. Please provide justification or explanation for this difference.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
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KEVIN B BUGIN
06/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203634 **INFORMATION REQUEST**

Santarus, Inc.
Attention: Maria Bedoya-Toro, PhD, MBA
3721 Valley Centre Drive, Suite 400
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for budesonide tablets, 9 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your responses by June 29, 2012. Please submit your responses via email to Catherine.TranZwanetz@fda.hhs.gov in addition to submitting as an amendment to your application:

A. Drug Substance

1. Please be advised that DMF # (b) (4) for Budesonide USP drug substance has been reviewed and is considered Not Adequate to support approval of this NDA at this time. A DMF Deficiency Letter has been sent to the DMF holder.

2. Report the specific results of the Residual Solvents tests for (b) (4) (b) (4) that are performed as part of the drug substance specification, rather than reporting (e. g. for (b) (4)) "NMT (b) (4) ppm".

B. Drug Product

3. In your acceptance specification for Talc USP, please include a test and acceptance criterion for Absence of Asbestos per USP monograph.

4. Please provide calculations for the following:
   - Assay / Related Substances of budesonide in the drug product;
   - HPLC procedure for determination of budesonide in the Dissolution media;
   - Determination of residual solvent ethanol in the drug product.

5. Please provide a chromatogram obtained under the conditions of your drug product Assay/ID/Related Substances procedure showing the elution of all specified impurities in

both the drug substance and drug product specifications including the API, budesonide. If any of the peaks co-elute, explain how the levels of those substances will be determined.

Also, the structure provided for [redacted] impurity ([redacted]) in sec. 3.2.P.5.5 of the NDA (Impurities) appears to be incorrect. Please revise.

6. The proposed limits in the drug product specification for [redacted] impurity (each [redacted]%) could result in a Total Daily Intake (TDI) of each impurity of [redacted] µg. This exceeds the ICH Qualification Threshold. Either provide data to qualify these impurities at the proposed levels, or tighten the acceptance criteria so that their TDI is below [redacted] µg.

7. Identify the specific materials (including the material that is in contact with the drug product) comprising the induction seal used in the container closure system intended for commercial use (HDPE bottle and cap). Also, identify the material that is in contact with the drug product after the induction seal is breached. The information should include references to Title 21 of the CFR indicating that these materials are acceptable as contact material for food. If this information is contained in a Drug Master File (DMF), provide a letter of authorization (LOA) that will allow access to the DMF.

8. Provide the following information for the physician sample blister pack: supplier of the blister pack; identification of the drug contact materials used in the blister pack (with references to Title 21 of the CFR indicating that the materials are acceptable as a contact materials for food); supplier(s) of the drug contact materials used in the blister pack; LOA for any DMF which contains this information.

9. Submit the complete executed batch record (EBR) for tablet lot AA062. The format of the EBR submitted for tablet lot AA062 in sec. 3.2.R1 of the NDA appears to be completely different from that of the MBR submitted in the same section.

10. There is no method validation package submitted to this NDA. Submit a Method Validation Package as described in 21 CFR §314.50(e)(2)(i).

C. Label / Labeling

11. The name of this drug product should be expressed in the label as follows:
"Uceris® (budesonide) Extended Release Tablets".

The term "MMX" is not acceptable as a part of the established name.

12. Provide container and carton labeling for the proposed physician sample blister pack.

If you have any questions, contact Cathy Tran-Zwanetz, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
05/31/2012
Chief, Branch IV

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide MMX) - Clinical Request for Information - May 23, 2012
Date:	Wednesday, May 23, 2012 8:19:25 AM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical sections of your submission and have the following comments and information requests. We request prompt written response in order to continue evaluation of your NDA.

1. For Study CB-01-02/02 please perform an analysis of remission rates for each of the following subgroups (non-responder imputation should be used for dropouts only):

a. All randomized patients *without* GCP violations
b. All randomized patients *without* GCP violations and *with* "positive histology"
c. All randomized patients *without* GCP violations and *with* "normal histology"

2. In addition, for Study CB-01-02/02, provide in the populations defined above (in a, b and c) analyses based on the following criteria:

a. Age (<65 vs. ≥65)
b. Race
c. Smoking status (ex-smoker vs. smoker vs. non-smoker)
d. Country
e. Baseline UCDAI score (4 vs. 5 vs. 6 vs. 7 vs. 8 vs. 9 vs. 10)
f. Baseline CRP (<10 mg/L vs. ≥10 mg/L)
g. Concomitant medication use status

[categories of concomitant medication use are: (1) concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) vs. (2) concomitant non-topical corticosteroids vs. (3) concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) and/or concomitant non-topical steroids vs. (4) neither concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) nor concomitant non-topical steroids]

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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/s/

KEVIN B BUGIN
05/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203634

GENERAL ADVICE

Santarus, Inc.
Attention: Maria Bedoya-Toro, Ph.D., M.B.A.
Vice President, Regulatory Affairs and Quality Assurance
3721 Valley Centre Drive, Ste. 400
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) dated December 14, 2012, received December 16, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Uceris (budesonide) 9 mg tablets.

We also refer to your amendments dated March 5, 2012, and April 25, 2012, requesting a waiver from conducting a Thorough QT (TQT) study to support your application for NDA 203634.

We have reviewed the amendments and agree that a TQT study is not needed for the following reasons:

- Budesonide (capsules) is being marketed since 1997. The C_{max} with the approved formulation ENTOCORT EC is slightly higher than that observed with budesonide MMX (tablets).

- No AEs of concerns as per ICH E14 Guidance have been reported post-marketing.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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ANDREW E MULBERG
05/16/2012

From:	Bugin, Kevin
To:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com)
Cc:	Bugin, Kevin; Matthew Moran (MMoran@santarus.com)
Subject:	NDA 203634 Uceris (budesonide MMX) - Statistics Request for Information - April 30, 2012
Date:	Monday, April 30, 2012 3:40:31 PM

Hi Maria,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the statistical sections of your submission and have the following comments and information requests. We request prompt written response in order to continue evaluation of your NDA.

1. For each study separately (Study CB-01-02/01 and Study CB-01-02/02) and combined, please perform an analysis of remission rates for the overall ITT population (all patients randomized). Also, perform analyses in the following two subgroups: "positive histology" only, and "normal histology" only subgroups. (Non-responder imputation should be used for dropouts only.)

2. Also, for each study separately (Study CB-01-02/01 and Study CB-01-02/02) and combined, provide in the populations defined above (ITT population, "positive histology" subgroup, and "normal histology" subgroup) analyses based on the following criteria:
    a. Age (<65 vs. ≥65)
    b. Race
    c. Smoking status (ex-smoker vs. smoker vs. non-smoker)
    d. Country
    e. Baseline UCDAI score (4 vs. 5 vs. 6 vs. 7 vs. 8 vs. 9 vs. 10)
    f. Baseline CRP (<10 mg/L vs. ≥10 mg/L)
    g. Concomitant medication use status
    [categories of concomitant medication use are: (1) concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) vs. (2) concomitant non-topical corticosteroids vs. (3) concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) and/or concomitant non-topical steroids vs. (4) neither concomitant immunosuppressants (i.e., azathioprine, MTX, or 6-MP) nor concomitant non-topical steroids]

3. Please provide timelines for Studies CB-01-02/01 and CB-01-02/02 including dates of major amendments to the protocols and Statistical Analysis Plans, date of first patient enrollment, date of last patient enrollment, and date of database lock.

Please let us know when you believe you can respond to the above. If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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KEVIN B BUGIN
04/30/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide MMX) - Clinical/Statistics Request for Information - April 23, 2012
Date:	Monday, April 23, 2012 5:30:46 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical and statistical sections of your submission and have the following comments and information requests. We request prompt written response in order to continue evaluation of your NDA.

For Study CB-01-02/01 and Study CB-01-02/02:

1. Provide specific details on what the GCP violations were (i.e. exactly what were the problems with data integrity) for your pivotal studies.

2. Describe exactly what criteria were used to define "normal histology".

3. For all patients excluded from your ITT population defined as all patients randomized (patients with normal histology, infectious colitis and GCP violations), please provide a tabulation (and SAS XPT data file) of:

   Patient ID #
   Country and study site
   Treatment group
   Demographic Data
   Criteria used to define active UC
   UC history
   Each Histology finding (with number of days into study included)
   Each UCDAI score (with number of days into study included)
   # of days into study when patient was excluded
   Indicator variable denoting if Normal histology. (yes/no)
   Indicator variable denoting if GCP violation. (yes/no)
   Indicator variable denoting if infectious colitis (yes/no)

We request that you respond to this request for additional information, no later than May 04, 2012. If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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/s/

KEVIN B BUGIN
04/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203634

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Santarus, Inc.
3721 Valley Centre Drive
Suite 400
San Diego, CA 92130

ATTENTION: Mathew E. Moran
Senior Director, Regulatory Affairs

Dear Mr. Moran:

Please refer to your New Drug Application (NDA) dated December 14, 2011, received December 16, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Budesonide Tablets, 9 mg.

We also refer to your January 19, 2012, correspondence, received January 20, 2012, requesting review of your proposed proprietary name, Uceris. We have completed our review of the proposed proprietary name, Uceris and have concluded that it is acceptable.

The proposed proprietary name, Uceris will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 20, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Kevin Bugin at (301) 796-2302

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/17/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide MMX) - Statistics Request for Information - March 01, 2012
Date:	Thursday, March 01, 2012 2:58:12 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the statistical sections of your submission and have the following comments and information requests. We request prompt written response in order to continue evaluation of your NDA.

1. It was found that for Study CB-01-02/01 and Study CB-01-02/02, the ITT population defined in the clinical reports deviated from that defined in the protocols and Statistical Analysis Plan.

    a. Provide the protocol specified ITT analysis of primary efficacy endpoint for Study CB-01-02/01 and Study CB-01-02/02.

    b. Explain why the ITT population defined in the clinical reports deviated from that defined in the protocols and Statistical Analysis Plan.

If you have questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
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KEVIN B BUGIN
03/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203634

FILING COMMUNICATION

Santarus, Inc.
Attention: Maria Bedoya-Toro, Ph.D., M.B.A.
Vice President, Regulatory Affairs and Quality Assurance
3721 Valley Centre Drive, Ste. 400
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) dated December 14, 2012, received December 16, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Uceris (budesonide) 9 mg tablets.

We also refer to your amendments dated January 20, 2012, January 27, 2012, February 10, 2012, and February 24, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 16, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 12, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights of Prescribing Information:

1. Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information [see 21 CFR 201.56(d)(3)].
2. The required verbatim statement, "**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)**" is duplicated in the SPL version of the labeling and should be corrected. [see 21 CFR 201.57(a)(1)]
3. 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. [see 21 CFR 201.57(a)(6)]
4. The required 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**" is duplicated in the SPL version of the labeling and should be corrected. [see 21 CFR 201.57(a)(11)(ii)]
5. There must reference to 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 (Patient Information)"
   [see 21 CFR 201.57(a)(14)]

We request that you resubmit labeling that addresses these issues by March 20, 2012. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a (b) (4) studies for this application. As noted in the FDA information request dated February 13, 2012, we do not agree with the rationale you have provided for a request for a (b) (4). Within 30 days of the date of this letter, submit a partial waiver request and a pediatric development plan for the pediatric age groups not covered by a partial waiver request. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this application.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Gastroenterology and Inborn Errors Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, MD, FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
02/28/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide MMX) - Request for Information - Biopharm - January 30, 2012
Date:	Monday, January 30, 2012 2:03:12 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the quality-biopharmaceutics-sections of your submission and have the following comment/request for information. We request prompt written response in order to continue evaluation of your NDA.

1. Provide the detailed dissolution method development report, including the following information/data;
   - The complete dissolution profile data collected during the development and validation of the proposed dissolution method.
   - A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., solubility data for the drug substance across the pH range, selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method as most appropriate should be included in the report. The dissolution profile should be complete and cover at least (b) (4) of drug dissolved or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend using at least twelve samples per testing variable.
   - The dissolution data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified.
   - Also, include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
   - The chosen method should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance.

2. Provide complete dissolution profile data (individual, mean, SD, profiles) for the biobatches and the primary stability batches (at each tested stability time point).

We request that you respond to this request for information by February 14, 2012. If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
01/30/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide MMX) - Request for Information - January 30, 2012
Date:	Monday, January 30, 2012 11:20:29 AM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the quality sections of your submission and have the following comment/request for information. We request prompt written response in order to continue evaluation of your NDA.

- Please clarify your justification for your request for exclusion from having to prepare an Environmental Assessment (EA) for NDA 203634. The current justification references 21 CFR §25.31(a) which indicates that an EA is not required for actions that will not increase the use of the active moiety. However, no budesonide dosage form currently marketed carries the same indication that NDA 203634 does (induction of remission in patients with active, mild to moderate ulcerative colitis). It therefore appears that approval of NDA 203634 would increase the use of budesonide, at least in a theoretical sense. Please do one of the following: 1) clarify how approval of NDA 203634 would not increase the use of budesonide; 2) provide a different justification for your exclusion request; 3) submit an EA for NDA 203634.

We request that you respond to this request for information by February 14, 2012. If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
01/30/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide MMX) - Request for Information - January 24, 2012
Date:	Tuesday, January 24, 2012 1:46:31 PM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical sections of your submission and have the following comment/request for information. We request prompt written response in order to continue evaluation of your NDA.

- Please certify that all studies contained in the NDA submission were performed in compliance with guidelines for Good Clinical Practice (GCP) and were conducted under the supervision of an IRB, or IEC equivalent, with adequate informed consent procedures. For studies that were conducted outside of the GCP, please list.

We request that you respond to this request for information by February 14, 2012. If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
01/24/2012

From:	Bugin, Kevin
To:	Matthew Moran (MMoran@santarus.com)
Cc:	Maria Bedoya-Toro, Ph.D (MBedoya-Toro@santarus.com); Bugin, Kevin
Subject:	NDA 203634 Uceris (budesonide MMX) - Request for Information - January 23, 2012
Date:	Monday, January 23, 2012 10:46:01 AM

Hi Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uceris (budesonide MMX).

We are reviewing the clinical and clinical pharmacology sections of your submission and have the following comments and information requests. We request prompt written response in order to continue evaluation of your NDA.

- Please confirm that the formulation used for the clinical drug material in the phase 3 studies is the same as the to-be-marketed formulation.
- Please submit the bioanalytical method validation reports.
- Please submit the electronic datasets for PK studies CRO-PK-03-105 and CRO-PK-06-178.

We request that you respond to these requests for information by February 14, 2012. If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
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/s/

KEVIN B BUGIN
01/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203634

NDA ACKNOWLEDGMENT

Santarus, Inc.
Attention: Maria Bedoya-Toro, Ph.D., M.B.A.
Vice President, Regulatory Affairs and Quality Assurance
3721 Valley Centre Drive, Ste. 400
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Uceris (Budesonide MMX) 9 mg Tablets

Date of Application: December 14, 2011

Date of Receipt: December 16, 2011

Our Reference Number: NDA 203634

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 14, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN
12/27/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074882

MEETING MINUTES

Santarus, Inc.
Attention: Maria Bedoya-Toro, Ph.D., M.B.A.
Vice President, Regulatory Affairs and Quality Assurance
3721 Valley Centre Drive, Ste. 400
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Budesonide MMX Extended Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 31, 2011. The purpose of the meeting was to discuss the submission of a new NDA for Budesonide MMX.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C.
Regulatory Health Project Manager
Division of Gastrointestinal and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 31, 2011
Meeting Location: 10903 New Hampshire Avenue, White Oak Building 22, Conference Room 1315, Silver Spring, MD 20903

Application Number: IND 074882
Product Name: Budesonide MMX
Indication: Treatment of, and induction of remission in, patients with active mild to moderate ulcerative colitis
Sponsor/Applicant Name: Santarus, Inc

Meeting Chair: Donna Griebel, M.D.
Meeting Recorder: Kevin Bugin, M.S., R.A.C.

FDA ATTENDEES

Donna Griebel, M.D. Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joyce Korvick, M.D., M.P.H. Deputy Director, DGIEP
Anil Rajpal, M.D., Medical Team Leader, DGIEP
Aisha Peterson Johnson, M.D., MPH, MBA, Medical Officer, DGIEP
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Office of Translational Sciences
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer, OTS
Sushanta Chakder, Ph.D., Nonclincal Team Leader, DGIEP
Sruthi King, Ph.D., Nonclinical Reviewer, DGIEP
Mike Welch, Ph.D., Biometrics Team Leader, Office of Translational Sciences
Wen Jen Chen, Ph.D., Biometrics Reviewer, Office of Translational Sciences
Kevin Bugin, M.S., R.A.C., Regulatory Health Project Manager, DGIEP
Valerie Gooding, Division of Regulatory Review Support, electronic Submission Support Team

SPONSOR ATTENDEES

Bob Bagin, Ph.D., Senior Director, Biostatistics and Data Management, Santarus, Inc.
Maria Bedoya-Toro, Ph.D., M.B.A., Senior Vice President, RA & QA, Santarus, Inc.
E. David Ballard II, M.D., Senior Vice President, Med. Affairs & Pharmacovig., Santarus, Inc.
(b) (4)
(b) (4)

Michael Huang, M.D., Medical Director, Clinical Research, Santarus, Inc.
(b) (4)

Matthew Moran, Senior Director, Regulatory Affairs, Santarus, Inc.
Luigi Moro, Chief Scientific Officer and R&D Director, Cosmo Technologies Ltd
Gerald Proehl, President & Chief Executive Officer, Santarus, Inc.
(b) (4)

1.0 BACKGROUND

On March 28, 2011, Santarus, Inc requested a meeting with the Agency to discuss the submission of a new NDA to the Division of Gastroenterology and Inborn Errors Products for Budesonide MMX extended release tablets for the treatment of, and induction of remission in, patients with active mild to moderate ulcerative colitis.

The key objectives of the meeting were to reach and capture agreements related to the results from the two Phase III, Multicentre, Randomized, Double-Blind, Double Dummy, Placebo-Controlled, Studies (U.S. Study CB-01-02/01 and E.U. Study CB-0102/02) and the companion study CB-01-02/06; the analysis plans for the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS); and Santarus's proposal to submit the data from Study CB-01-02/04 (12 month extension study evaluating safety and efficacy of maintenance therapy with budesonide MMX 6 mg) as part of the 120-Day Safety Update to the Original NDA submission.

The meeting took place as scheduled on May 31, 2011and the following minutes reflect the agreements and discussion of that meeting.

2. DISCUSSION

[The Sponsor's original questions are in plain font. The Division's preliminary comments is in **Bold** font and discussion from the meeting is in ***Bold italics.*** Where available, the Sponsor's response to Agency preliminary comments is also in ***Bold italics.***]

Medical

Question 1: It is Santarus' opinion that the two Phase III, Multicentre, Randomized, Double-Blind, Double Dummy, Placebo-Controlled, Studies (U.S. Study CB-01-02/01 and E.U. Study CB-01-02/02) provide substantial evidence for the safety, efficacy and clinical benefit of budesonide MMX in the induction of remission in patients with active mild to moderate ulcerative colitis. Santarus believes that the results from these studies are adequate for filing and review in a NDA. Does the agency agree?

FDA Response:
The final determination on the adequacy of an NDA for filing will be determined at the time of filing. Whether the two studies (U.S. Study CB-01-02/01 and E.U. Study CB-01-02/02) provide substantial evidence for the safety, efficacy, and clinical benefit of

budesonide MMX in the induction of remission in patients with active mild to moderate ulcerative colitis will be determined during the review period.

Discussion:
No further discussion.

Question 1a: The analyses of efficacy for the two pivotal studies were conducted in the prospectively defined ITT population according to the SAPs dated July 15, 2010. Additional post hoc sensitivity analyses included all randomized patients who received at least one dose of study drug, but those who had major entry criteria violations, GCP violations, or normal histology at baseline were analyzed as non-remitters. Analyses of efficacy in the ITT population as defined in the SAP dated July 15, 2010 and the supportive sensitivity analyses will be presented in the clinical study reports (CSRs) and ISE. Does the agency agree?

FDA Response:
We understand that you are planning to exclude 50 patients from your ITT analysis due to GCP violations and have read your rationale. Be advised that this is a review issue and as discussed in the April 13, 2010 meeting, we will consider the true ITT population as the primary analysis population. Furthermore, at this time we can not commit to having any alternative analysis serve as the basis for regulatory action without fully reviewing all the data.

Also, see additional comments below.

Santarus Response:
Santarus understands FDA's response regarding patients with GCP violations. However, FDA was silent on the issue of excluding patients with normal histology. Santarus would like to briefly present the medical rationale behind the exclusion of patients with normal histology and gain an understanding of FDA's thinking with regard to this issue.
Could the Agency clarify its position on the exclusion of patients with normal histology at baseline?

Discussion:
The Agency will review all of the data and will consider the proposed population (excluding patients with normal histology) in its determination of efficacy. This remains a review issue. The primary analysis population will remain the true ITT population.

Medical/Biometrics

Question 2: The ISE will include efficacy data from all patients from completed Phase II and III studies in the budesonide MMX clinical development program. Specifically, data from the two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02) will be combined and analyzed. Data

from the Companion Study (CB-01-02/06) and the two Phase II studies (CB-01-02/05 and CRO-03-53) will be also be summarized and discussed in the ISE. Does the agency agree?

FDA Response:
Your proposed ISE analysis plan appears to be acceptable and will be assessed during the review process. However, the data from the individual studies as analyzed in the clinical study reports are the main focus of review as these provide the basis for demonstration of efficacy. Results based on the ISE analyses are largely exploratory and not supportive for labeling purposes.

Discussion:
No further discussion.

Question 3: For the ISS, the following three analyses are planned:
First, a combined analysis of the data from the two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02) will follow the analyses of all safety endpoints as specified in the SAP for both studies. Second, a combined analysis of the data from all completed Phase II and III studies from the budesonide MMX clinical development studies including the two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02), the Companion study (CB-01-02/06), and the two Phase II studies (CB-01-02/05 and Cro-03-53) will evaluate safety by dosage strength and by duration of treatment. Third, a combined analysis of the three Phase I studies (CR-01-28, CROPK-06-178 and CROPK03105) will evaluate AEs, SAEs, physical examination results and laboratory results. Does the agency agree?

FDA Response:
Your proposal for the ISS appears reasonable.

Discussion:
No further discussion.

Question 4: Santarus proposes to submit the data from the currently ongoing Extension Study CB-01-02/04 (b) (4) Does the agency agree?

FDA Response:
All efficacy and safety data for labeling consideration must be submitted at the time of original NDA submission.

Santarus Response:
Santarus is currently seeking an induction of remission label claim for the 9 mg dose

- ***Santarus does not plan to*** (b) (4) (b) (4)

- ***The emphasis of the data from the 12 month extension study will be on safety***

Therefore, we would like to understand the rationale for the request to submit the data from the extension study at the time of the original NDA, (b) (4) (b) (4) ***Can the Agency please clarify?***

Discussion:
The Agency reiterated that we need to have any efficacy data with the original NDA submission for consideration of efficacy. The Agency also requests that the results of the 12-month extension study be included in the original NDA submission.

Question 5: Because the programming for the study reports for all studies and for the integrated summaries were conducted using SAS 99 compliant datasets, it is our intention to submit the CRF data and all analysis datasets in SAS 99 compliant format. It is also our intention to submit SDTM datasets for the four Phase III studies. Does the Agency agree?

FDA Response:
It is not clear what you mean by "SAS 99 compliant." Data sets must be submitted in the SAS XPORT Transport Format which is an open (non proprietary) format. Refer to the *Study Data Specifications* document for additional information provided at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf.

We recommend that you provide the following full case report tabulation (CRT) for each adequate and well-controlled clinical study (per 21 CFR 314.126) you plan to include in your NDA/BLA submission:

1. **All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file fully comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.**

   Discussion:
   No further discussion.

2. **All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, should be submitted along with a thorough data definition file. We recommend that these electronic datasets fully incorporate the modeling approaches described by both the latest CDISC/ADaM standard and the FDA Study Data Specifications document, cited above. We recommend that the data definition file fully comply with the latest CDISC/Define.XML standard.**

Discussion:
No further discussion.

3. **A well commented and organized software program written for each analysis dataset and efficacy table created.**

Discussion:
No further discussion.

Additional FDA Comments:

1. **Please refer to our statistics comments from the April 13, 2010 meeting. The issues discussed during that meeting are considered review issues and will be asses**

Discussion:
No further discussion.

2. **Your proposed Type I error control stated in section 9.5 ("Efficacy Analysis") of the protocol for the two pivotal studies (CB-01-02/01 and CB-01-02/02) is not clear. We recommend the significance level of 2.5% for the primary and secondary endpoints analyses be applied as a two-sided testing procedure because for each endpoint there are two study drug doses being compared with placebo.**

Discussion:
No further discussion.

3. **We recommend that you conduct an *in-vitro* study to evaluate whether budesonide is a substrate, inhibitor, or inducer of transporters. [Please refer to Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling, *DRAFT GUIDANCE.*]**

Santarus Response:
The effects of budesonide on p-gp transporters has already been investigated in-vitro in the literature. Santarus intends to submit the NDA as a 505(b)(2) application, referencing this budesonide literature. Based on this filing strategy, and the safety profile of budesonide, Santarus believes this additional study is unnecessary. Does the Agency concur?

Discussion:
Acceptability of literature to support the lack of an in vitro study to evaluate the effects of budesonide as a substrate, inhibitor or inducer of transporters will be a review issue.

4. **Please evaluate the effect of alcohol dose dumping on Budesonide MMX Extended Release Tablets.**

   Santarus Response:
   The budesonide MMX technology is similar to the technology utilized in Lialda® for UC. Unlike other delayed-release steroid formulations, which have only a pH-sensitive coating as a rate-limiting step for drug release, budesonide MMX also has the multi-matrix structure which is responsible for the extended release profile of the tablet. Even upon sudden dissolution of the coating, the multi-matrix structure ensures a slow, homogeneous release of drug over time. We are unaware of any safety signals related to this technology. Santarus would like to understand the Agency's rationale behind this request.

   Discussion:
   Alcohol dose dumping studies are required for all delayed release products. Santarus will provide dissolution data in the CMC sections of the NDA submission to support a justification for lack of dose dumping studies. Depending on the results of the in vitro studies, an in vivo study may be necessary

5. **We note that two of the Phase-1 studies (CRO-01-28 and CRO-PK-03-105) were conducted with only male healthy subjects, and only one Phase 1 study with single dose (CRP-PK-06-178) included both male and female healthy subjects in the study. If we observe PK differences due to gender in this single-dose study, we may ask for additional data (e.g., multiple dose and food effect studies) that include both male and female subjects.**

   Discussion:
   No further discussion.

6. **CDER's preferred electronic format for submitting a new application is eCTD format. Please refer to Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifcations. If this is your first eCTD submission, it is recommended that a sample eCTD be completed prior to submitting an actual submission, please refer to the eCTD Sample Web page or contact ESUB (esub@fda.hhs.gov) for more information."**

   Discussion:
   No further discussion.

7. **We note you refer to the Special Protocol Assessments (SPAs) for protocols CB-01-02/01 and CB-01-02/02; we remind you that no formal agreement was reached on these protocols following the Agency's comments sent on January 28, 2008. Please**

refer to Guidance for Industry-Special Protocol Assessment for further information (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf).

Santarus Response:
To address FDA's comments from January 28, 2008, the Sponsor requested a Type A Meeting which was held on March 7, 2008. Please see memorandum of meeting minutes dated April 4, 2008 (included in the pre-NDA meeting briefing package).

Discussion:
There were agreements in response to specific questions throughout the SPA review process and the April 04, 2008 meeting. These agreements are still valid. The Agency simply points out that no SPA agreement on the Protocol as a whole was reached.

3. ATTACHMENTS AND HANDOUTS

Santarus, Inc slide presentation attached.

17 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 74,882

Cosmo Technologies Limited
Attention: Young J. Choi,
Manager, Regulatory Affairs
ICON Development Solutions
6031 University Boulevard, Suite 300
Ellicott City, MD 21043

Dear Mr. Choi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CB-01-02 Budesonide MMX™ Extended Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2008. The purpose of the meeting was to further clarify our responses to your two Special Protocol Assessments (SPAs) for protocols CB-01-02/01 and CB-01-02/02.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 7, 2008
TIME: 3:00 PM – 4:00 PM EST
LOCATION: FDA White Oak Building 22, Conference Room 1311
APPLICATION: IND 74,882
DRUG NAME: CB-01-02 Budesonide MMX™ Extended Release Tablets
TYPE OF MEETING: Type A

MEETING CHAIR: John Hyde, Ph.D., M.D., Medical Team Leader

MEETING RECORDER: Heather Buck, MS, MBA

FDA ATTENDEES:

Joyce Korvick, M.D., M.P.H. Deputy Director, Division of Gastroenterology Products
John Hyde, Ph.D., M.D., Medical Team Leader, Division of Gastroenterology Products
Aisha Peterson, M.D., MPH, MBA, Medical Officer, Division of Gastroenterology Products
Jane Bai, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Milton Fan, Ph.D., Statistical Reviewer, Division of Biometrics 3
Kristen Everett, R.N., Regulatory Project Manager, Division of Gastroenterology Products
Heather Buck, Regulatory Project Manager, Division of Gastroenterology Products

COSMO TECHNOLOGIES LTD ATTENDEES:

Cosmo
Richard Jones, Ph.D., R&D Manager
Steven Kradjian, RAC, Regulatory Affairs Consultant for Cosmo
Luigi Moro, Chief Scientific Officer and R&D Director
Marco Cavaleri, Scientific Associate Director

(b) (4)

BACKGROUND:

We received IND 74,882 (containing one Special Protocol Assessment (SPA) request CB-01-02/01) and one concurrent SPA request CB-01-02/02) on November 30, 2007. IND 74,882 is for CB-01-02 Budesonide MMX™ Extended Release Tablets for the indication of treatment induction of remission in patients with mild to moderate ulcerative colitis. A Pre-IND meeting was held June 6, 2006.

This Type A meeting was requested February 8, 2008. We received the background package February 21, 2008. We received a correction to Reference 3 of the background package on March 3, 2008. We sent preliminary responses to Cosmo March 5, 2008.

MEETING OBJECTIVES:

The main objective is for Cosmo to receive clarification on three areas relating to the SPA submission and response referred to above. These include:

- Rationale and approach for dose determination and treatment duration selection
- Approach to collect maintenance data in an extended Phase 3 protocol
- Rationale and timing for clinical follow-up visit

DISCUSSION POINTS:

Discussion questions and answers follow. FDA responses are in **bold**, and meeting discussion is in ***bold italics***.

1. Rationale and approach for dose determination and treatment duration selection.

    a. Would including a 6 mg/OD in both pivotal studies CB-01-02/01 and CB-01-02/02 constitute a valid alternative to the conduct of a Phase II dose-ranging study prior to the initiation of Phase III studies?

    FDA Response
    There is no regulatory requirement to conduct Phase 2 studies, but without them, we have no firm basis for endorsing a particular dose. Because ulcerative colitis (UC) is a new indication for budesonide, and because the release characteristics of your product are different from those of Entocort EC, a dose ranging study will be helpful. It may be more efficient to do dose exploration in a smaller Phase 2 study, but if you are planning instead to include the 6 mg dose in both Phase 3 studies, that also would be informative.

    Meeting Discussion
    Cosmo agreed that it may be more efficient to do dose exploration in a smaller Phase 2 study, however the Phase 3 plan now will include the 6 mg dose in both Phase 3 studies. FDA stated that this was an acceptable approach, but noted that this agreement was limited to agreement with the plan to include dose exploration in both studies; FDA reserves the right to critique choice of dose when the study results come under review

    b. Would including a treatment duration of 8 weeks in both pivotal studies, with the primary endpoint (UCDAI) at 8 weeks, but still including full clinical assessment

(CAI) at 2, 4, and 8 weeks as secondary endpoints in both studies, be considered an adequate and agreeable approach to treatment duration selection?

FDA Response

An eight week treatment duration appears reasonable; primary endpoints at six weeks or eight weeks have been used in the UC induction studies of several products approved for UC. However, the choice of treatment duration is up to you. A Phase 2 study could be used to estimate the rate of onset of activity, which could be helpful in selecting the most advantageous time for the primary endpoint assessment. As mentioned in the pre-IND meeting and our SPA responses, in the absence of a complete Phase 2 development program, we have no firm basis for evaluating the adequacy of the choice of eight weeks as the treatment duration.

If you plan to propose labeling claims based a secondary endpoint defined in terms of the CAI, which does not involve endoscopy, you will need to provide adequate validation of that endpoint. Also, if you propose to use the results of a secondary endpoint analysis to support labeling claims, the analysis should be clearly pre-specified with a detailed analysis plan that preserves the Type I error.

Meeting Discussion

Cosmo accepted FDA's response regarding treatment duration and will plan to proceed with an eight week treatment duration. They referenced their Phase 2 study (Study Report CRO-03-053), which is summarized in Reference 10 of the Background Package. The selection of 8 weeks for treatment evaluation is based on Cosmo's data from this Phase 2 study, which compared endoscopic and histological changes at 4 weeks and 8 weeks.

Cosmo accepted FDA's response regarding labeling claims based on a secondary endpoint defined in terms of CAI. Cosmo intends to use the CAI score for a clinical remission secondary endpoint only. FDA reiterated that the use of the definition for that clinical endpoint would need adequate justification.

Cosmo also appreciated FDA's comment that the analysis should be clearly pre-specified with a detailed analysis plan that preserves the Type 1 error. They referenced page 58 of the current proposed US Phase 3 protocol CB-01-02/01, Attachment 5 in the Background Package, where five secondary endpoints considered to be major are described in hierarchical order. They have specified the statistical methodology to be applied to the secondary endpoint analysis, taking into account preservation of alpha Type 1 error. Cosmo will submit a detailed statistical analysis plan to the IND after the protocol enrollment begins, but prior to initiating the statistical analysis.

FDA requested that the statistical analysis plan (SAP) be submitted for review by the statistical review team. FDA advised that the SAP should be formulated as early as possible, rather than waiting until just before conducting the analysis, to avoid raising questions of whether it includes post-hoc analyses.

2. After demonstrating safety and efficacy of Budesonide MMX™ in the initial indication of Budesonide MMX™ in maintenance of remission in separate dedicated studies (b) (4)

Would the Agency agree on Sponsor's plan initially to seek approval of an NDA with the initial indication of induction of remission only, based on the current trials CB-01-02/01 and CB-01/02/02 and an extension of either of these trials to capture maintenance data to support writing adequate instructions for use on the management of the chronic disease?

FDA Response
We ask that you submit a marketing application for evaluation that includes enough data for comprehensive labeling at the time of initial submission. An eight week induction study alone does not answer all the questions needed for clinicians to know how to use the product in patients. Because UC is a chronic disease, questions of how the drug should be used in induction, maintenance, and repeat therapy should be answered in the initial application.

Meeting Discussion
Cosmo commented that the proposed Phase 3 study in the US is intended to be followed by a double-blind extension phase maintenance study in approximately 150 patients for 6 months at a dose of 6 mg versus placebo. The data from this extension study will be included in the NDA submission and is intended to support the indication of induction of remission. Cosmo considers the maintenance indication as distinct from the induction of remission indication.

FDA agreed in general with Cosmo's plans to support an indication for induction of remission, however FDA felt that an NDA would also need to address chronic treatment of UC using the product. UC is a chronic disease, and therefore to support writing adequate instructions for use, a NDA should include instructions for how patients should be treated in the long term. FDA clarified that this did not mean that continuous therapy needed to be studied; episodic re-treatment for flairs might be the appropriate use of the drug. But some manner of using the drug in the chronic management of UC should be proposed and evaluated. Ideally, an NDA would be expected to include a reasonable dataset that evaluated the safety and efficacy of the proposed manner of use for one year. In response to Cosmo's question of whether (b) (4) ***FDA strongly recommend that a complete initial application be submitted.***

Cosmo stated that if they find that the drug is not appropriate for maintenance of remission, they would not pursue this route. FDA emphasized that "maintenance" can

be thought of as including re-treatment therapy, and it would still be appropriate to attempt to evaluate some form of chronic management strategy.

3. The Sponsor is not attempting to assess duration of remission of relapse rates with the proposed 2 week post treatment follow-up visit in both trials. Would a clinical follow-up visit at 2 weeks following end of treatment be considered long enough for the assessment of safety only in the context of a clinical program aimed at supporting the indication of induction or remission only?

FDA Response

Please also see response to Question 2. We strongly recommend that you expand your development program to include the consideration of maintenance therapy, and design the post-induction follow-up with attention to the proposed plans for how maintenance therapy would be given. Ideally, one or more of your induction studies could be integrated with studies of maintenance. That could provide a ready resolution of the question of how to conduct post-induction follow-up.

With your current design, the four-week visit to assess rates of relapse should involve collection of data pertaining to disease activity, which will likely require more than a telephone query of patients. Patients with significant side effects (including those related to adrenal suppression) need to be followed to resolution. Also, you will need to answer the question of how patients with adrenal suppression will be managed. Will they be switched to another medication or continued on the study drug? We encourage you expand the duration of your follow-up to begin to obtain some information about the time to relapse.

Meeting Discussion

(See also discussion for preceding question and response).

Cosmo has committed to conduct an extension phase protocol with the proposed US Phase 3 protocol CB-01-02/01; the time to relapse will be captured in approximately 150 patients who are expected to participate in this extension study.

Regarding the four-week visit to assess relapse and the plans to evaluate side effects, Cosmo referenced Section 6.5 on page 44 of Protocol CB-01-02/01 (at Attachment 5 of the Background Package). The two-week visit in the currently proposed protocol includes an abbreviated physical exam, review and record of AE's, and evaluation of glucocorticoid-related effects, specifically including moon face, sleep changes, striate rubrae, insomnia, flushing, acne, fluid retention, hirsutism, and mood change. Serious adverse events will be followed to resolution. Cosmo committed to amend the protocol at Section 6.5 to include the requirement to follow significant steroid-related affects until four weeks after the end of treatment.

FDA commented that it is acceptable to follow serious or other significant adverse reactions until they are resolved or stabilized (as some may not resolve).

Additional Discussion Items
FDA recommended that the definition for remission also include the requirement that there be a finding of no friability on endoscopy.

Cosmo asked if the FDA would be issuing some kind of letter stating the agreements that were reached, and whether it would be advisable to request another Special Protocol Assessment (SPA). FDA responded that there would be no special agreement letter; the letter they will send will contain the FDA's minutes of this meeting, which would reflect agreements made at the meeting. FDA commented that the most effective use of a SPA would be to ensure that there was clear and complete understanding about certain critical elements of a particular protocol, and that SPA questions ideally should focus on specific important issues of that protocol's design. Broad questions about the general acceptability of a protocol carry the risk that any SPA agreement could be invalidated by subsequent protocol amendments. An SPA would not be a mechanism for obtaining agreement about a development program. If Cosmo feels that their questions have been answered acceptably, they are satisfied with the degree of understanding about the issues, and the meeting minutes adequately reflect the agreements, then there may not be much to be gained by requesting a SPA.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

The main change that Cosmo agrees to make to the protocol is to follow adverse events until they are stabilized.

ATTACHMENTS/HANDOUTS:

Cosmo handed out their comments to our preliminary answers, which have been incorporated in the minutes herein.

Linked Applications	Sponsor Name	Drug Name
`ID 74882	COSMO TECHNOLOGIES LTD	CB-01-02 BUDESONIDE MMX

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

/s/

JOHN E HYDE
04/04/2008