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RESEARCH**

APPLICATION NUMBER:

205613Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA # 205613

Product Name: _____

PMR/PMC Description: A 6-week randomized, double blind, placebo-controlled trial in children 5 to 17 years of age with active, mild to moderate distal ulcerative colitis (extending up to 40 cm from the anal verge). The trial will evaluate pharmacokinetics (PK), efficacy for induction of remission, and safety of at least 2 doses of Uceris (budesonide) Rectal Foam. The effects of 6 weeks of Uceris (budesonide) Rectal Foam on the HPA axis will be assessed.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	04/2015
	Study/Trial Completion:	01/2018
	Final Report Submission:	04/2018
	Other:	N/A

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

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

PREA does not apply to the adult indication as the pediatric indication has orphan status (designation date of May 6, 2013¹). It should be noted that despite the technical difference in the wording of the sponsor's proposed indication of (b) (4) and the orphan indication, the proposed indication (b) (4) (b) (4)

Therefore, this is a postmarketing commitment.

¹http://www.accessdata.fda.gov/scripts/opdlisting/ood/OOPD_Results_2.cfm?Index_Number=394613 (accessed August 25, 2014)

²E-mail from Erica Radden PMHS Reviewer dated July 25, 2014.

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

See the description in Section 1.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

See the description in Section 1.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

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

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

Jeanine Best, MSN, RN, PNP, Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

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

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

Drug: Uceris (budesonide) rectal foam

Application number: NDA 205613 (IND 104725)

Re: Pediatric Waiver Request and Labeling Review

Sponsor: Salix Pharmaceuticals, Inc.

Proposed Indication: Induction of remission in (b) (4) patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

Proposed Dosage Form & Route of Administration: Rectal foam; 2 mg budesonide per metered dose for rectal administration only

Proposed Dosing Regimen: The recommended dosage is 1 metered dose administered twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks.

Consult request:

DGIEP requests the Pediatric and Maternal Health Staff (PMHS) to review the proposed pediatric study plan and assist in preparation for the Pediatric Review Committee (PeRC) meeting. Also, DGIEP requests PMHS' assistance with labeling related to pregnancy, lactation and pediatrics.

Materials Reviewed:

- PMHS Consult Request (December 10, 2013)
- Background packet for budesonide rectal foam including the Pediatric Study Plan and Full Waiver Request (November 15, 2013)
- Previous PMHS consult reviews for Uceris (budesonide MMX), IND 118,972 (October 24, 2013)
- Proposed Uceris (budesonide) rectal foam labeling (November 15, 2013)
- Current approved Pulmicort Flexhaler (budesonide inhalation powder) labeling (July 2, 2010)

Regulatory Background:

On November 15, 2013, Salix Pharmaceuticals, Inc. submitted NDA 205613 for budesonide rectal foam, a rectally administered glucocorticosteroid with the proposed indication of induction of remission in patients with active mild to moderate distal ulcerative colitis (UC) extending up to 40 cm from the anal verge. Of note, Salix Pharmaceuticals, Inc. acquired Santarus, Inc. in January, 2014. An extended release oral budesonide tablet, Uceris (Santarus, Inc.), was approved on January 14, 2013 for the induction of remission in mild-to-moderate, active UC. According to the approval letter, pediatric study requirements for patients less than 5 years were waived because studies are impossible/highly impracticable based on the low incidence of disease in this age group. The following pediatric study was deferred:

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 Report Submission: 09/2016)

Following approval for Uceris tablets, Santarus, Inc., applied for orphan designation for Uceris (budesonide) for the treatment of UC in pediatric patients 0 to 16 years of age. Orphan designation was granted on May 18, 2013. Therefore, the pediatric study requirement that was issued at the time of approval of Uceris tablets remains in effect. (See further discussion on this orphan designation relative to the pediatric study requirements for this current Uceris rectal foam application below.)

(b) (4)



(b) (4)



However, the orphan designation granted for Santarus, Inc. for Uceris (budesonide) is applicable to any dosage form, and because Salix Pharmaceuticals, Inc. acquired Santarus, Inc., the designation applies to this application. Furthermore, following discussion with the Orphan Drug Products and DGIEP, PMHS agrees that the proposed indication of distal ulcerative colitis (or (b) (4)) is a subset of the orphan indication of pediatric ulcerative colitis, and thus, this product has orphan designation for the pediatric population. Additionally, because orphan products are exempt from the Pediatric Research Equity Act (PREA), pediatric study requirements are not applicable to budesonide rectal foam. However, a Written Request should be considered.

DGIEP has consulted PMHS to review and provide feedback on the submitted pediatric plan. However, because this product has orphan designation and is exempt from PREA, a pediatric plan is not required. DGIEP also requested assistance with labeling regarding pregnancy, nursing and pediatrics and comments on labeling are provided below.

PMHS Review of labeling:

Pregnancy and Nursing Mothers Labeling:

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the

available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

Pediatric Use Labeling:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products granted pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

See Appendix 1 for proposed sponsor labeling for Uceris (budesonide) rectal foam dated November 15, 2013.

Discussion on Labeling Recommendations:

Pregnancy and Nursing Mothers Labeling

PMHS-MHT conducted a review of literature using DRUGDEX and REPRORISK-MICROMEDEX, and LACTMED-TOXNET databases regarding pregnancy and lactation for budesonide. Labeling recommendations related to pregnancy and lactation are provided here and are structured in order to provide clinically relevant information for prescribing decisions and also to comply with current regulatory requirements.

Adequate and well controlled studies have not been performed with rectally administered budesonide in pregnant women. Additionally, literature review of the DRUGDEX and REPRORISK-MICROMEDEX databases revealed no data on the use of budesonide rectal foam in pregnancy. However, the following data on the use of inhaled corticosteroids in the treatment of persistent asthma during pregnancy was included in the Pulmicort Flexhaler (budesonide inhalation powder) labeling (July 2, 2010). In a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (i.e., Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) no increased risk for congenital malformations from the use of inhaled budesonide during the first trimester of pregnancy was observed. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in the first trimester of pregnancy, and the rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal

population (4 children vs. 3.3, respectively). In a second study utilizing the same data, the incidence of congenital malformation in infants whose mothers were exposed to inhaled budesonide (n=2534) did not differ from the rate for all newborn babies during the same period (3.6% vs 3.6%).¹

Animal reproduction studies have been conducted with subcutaneous administration of budesonide which demonstrated skeletal abnormalities, fetal loss and decreased pup weight in rats and rabbits at doses 1.2 times and 0.12 times, respectively, of the human intrarectal dose of 4 mg/day. Additionally, when budesonide was administered to rats by inhalation at doses up to approximately equivalent to the maximum recommended daily inhalation dose [720mcg twice daily] in adults on a mcg/m² basis, no teratogenic or embryocidal effects were observed.¹ Due to the potential for fetal harm based on data from animal studies and the lack of human data, budesonide rectal foam should be administered to pregnant women only if the potential benefit outweighs the potential risk to the fetus.

The LACTMED-TOXNET database² contains a summary of the use of inhaled budesonide during lactation from available published data. Maternal milk levels and infant serum levels are provided. Maternal milk levels were minute compared to the dose of budesonide administered and infant serum levels were below the level of detection with the assay used. Based on the published maternal milk levels, a fully breastfed infant would receive a maximum of 0.3% of the weight-adjusted inhaled maternal dosage, assuming 100% oral bioavailability from breastmilk. However, data demonstrate that orally administered budesonide is only about 9% bioavailable; therefore, bioavailability in a breastfed infant would also be expected to be low. Available pharmacokinetic data demonstrate low budesonide plasma levels in adults following rectal administration; therefore, budesonide levels in breast milk are also expected to be low as other routes of administration have not demonstrated sequestration or higher levels in breastmilk. Consequently, the potential risks of glucocorticoid exposure (e.g., adrenal suppression, hypercorticism, immunosuppression, and in pediatric patients, reduction of growth velocity) appear unlikely with exposure through breastmilk. The American Academy of Pediatrics (AAP) considers breastfeeding to be the ideal method of feeding and nurturing infants.³ In addition, human milk is the most complete form of nutrition for infants and offers a range of health benefits for lactating women and breastfed infants. Breastfeeding should not be discouraged with drug use unless appropriately justified. The available budesonide lactation data with other routes of administration do not justify discouraging breastfeeding in lactating woman using budesonide for labeled uses. Therefore, nursing mothers labeling for Uceris rectal foam should advise prescribers to exercise caution when administering the drug to a lactating woman, not discourage breastfeeding with drug use.

¹ Current Pulmicort Flexhaler (budesonide inhalation powder) labeling, dated July 2, 2010

² See <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~v8zMS9:1>

³ American Academy of Pediatrics Policy Statement. "Breastfeeding and the Use of Human Milk." Pediatrics. 2012; 129: e827-e841

The sponsor proposed a pregnancy category C classification⁴ which accurately reflects the adverse effects noted in animal reproduction studies and the lack of adequate and well-controlled studies in pregnant women. PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy. Additionally, the precautionary language included in the Pregnancy subsection should also be reflected in Highlights/Use in Specific Populations/Pregnancy.

Pediatric Use Labeling

The current proposed statement of use language for the Pediatric Use subsection is appropriate because budesonide rectal foam has not been studied or approved for use in the pediatric population. Given the possibility of off-label use of rectal budesonide in pediatric patients, PMHS recommends additional language based on class warnings related to systemic absorption of corticosteroids in pediatric patients in labeling for other corticosteroid drugs. [REDACTED] (b) (4)

Conclusion:

The sponsor was granted orphan designation for budesonide for pediatric ulcerative colitis, and therefore, PREA does not apply.

PMHS-MHT structured the Pregnancy and Nursing Mothers subsections of Budesonide rectal foam labeling in the spirit of the proposed PLLR, while complying with current labeling regulations. Recommended labeling for the pediatric population is provided below per 21 CFR 201.57(c)(9)(iv).

PMHS Actions:

PMHS reviewed the briefing packet and participated in the internal meetings from January to August, 2014. PMHS provided feedback [REDACTED] (b) (4). Our input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

⁴ Pregnancy Category C - Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well controlled (AWC) studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.

⁵ SEALD labeling review tool.

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

PMHS Recommended labeling for Uceris (budesonide) rectal foam:

HIGHLIGHTS OF PRESCRIBING INFORMATION

USE IN SPECIFIC POPULATIONS

- [REDACTED] (b) (4)

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with UCERIS in pregnant women. Animal reproduction studies have been conducted with UCERIS. In these studies, subcutaneous administration of budesonide to rats and rabbits at doses 1.2 times and 0.12 times, respectively, the human intrarectal dose of 4 mg/day, produced skeletal abnormalities, fetal loss and decreased pup weight. UCERIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4 percent for major malformations, and 15 to 20 percent for pregnancy loss.

Clinical Considerations

Fetal/neonatal adverse reactions

Hypoadrenalism may occur in neonates exposed to glucocorticosteroids *in utero*. Carefully, observe these neonates for signs and symptoms of hypoadrenalism.

Animal Data

Budesonide is teratogenic and embryocidal in rabbits and rats. [REDACTED] (b) (4)

[REDACTED] (approximately 0.12 times the recommended human intrarectal dose of 4 mg/day, based on the body surface area)

[REDACTED] (b) (4) In a subcutaneous embryofetal development study [REDACTED] (b) (4)

8.3 Nursing Mothers

UCERIS is likely present in human milk as budesonide delivered by inhalation from a dry powder inhaler is present in human milk at low levels. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for UCERIS and any potential adverse effects on the breastfed child from UCERIS or from

the underlying maternal condition. Exercise caution when administering UCERIS to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of UCERIS in pediatric patients have not been established. Children who are treated with corticosteroids by any route may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been in the absence of laboratory evidence of HPA axis suppression. The long-term effects of this reduction in growth velocity associated with corticosteroid treatment, including the impact on final adult height, are unknown. Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in children than some commonly used tests of HPA axis function. The linear growth of children treated with corticosteroids by any route should be monitored (e.g., via stadiometry), and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of other treatment alternatives. In order to minimize the potential growth effects of corticosteroids, children should be titrated to the lowest effective dose.

**Appendix 1: Proposed Sponsor Labeling for Uceris (budesonide) rectal foam
(November 15, 2013)**

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)





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/s/

ERICA D RADDEN
08/26/2014

JEANINE A BEST
08/26/2014

HARI C SACHS
08/26/2014

LYNNE P YAO
09/03/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 13, 2014

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors Products
(DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name)
Dosage Form and Route: UCERIS (budesonide) Rectal Foam

Application Type/Number: NDA 205613

Applicant: Salix Pharmaceuticals, Inc.

1 INTRODUCTION

On November 15, 2013, Salix Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) 205613 for UCERIS (budesonide) Rectal Foam with the proposed indication for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on January 23, 2014 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for UCERIS (budesonide) Rectal Foam.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

2 MATERIAL REVIEWED

- Draft UCERIS (budesonide) Rectal Foam PPI and IFU received on November 15, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 31, 2014.
- Revised draft UCERIS (budesonide) Rectal Foam PPI and IFU received by DMPP and OPDP on August 8, 2014.
- Draft UCERIS (budesonide) Rectal Foam Prescribing Information (PI) received on November 15, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 31, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
08/13/2014

MEETA N PATEL
08/13/2014

BARBARA A FULLER
08/14/2014

LASHAWN M GRIFFITHS
08/14/2014

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 13, 2014

To: Kelly Richards, RN, MSN
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205613
OPDP Comments for draft Uceris Rectal Foam PI

OPDP has reviewed the proposed draft PI for Uceris Rectal Foam. We have reviewed the draft PI, retrieved from Sharepoint on August 4, 2014, and have the following comments. Comments on the draft PPI and IFU will be provided under separate cover.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
08/13/2014



Memorandum

DATE: March 4, 2014

CONTACT: KEVIN BUGIN (CDER)
ZANA MARKS (CDER)

FROM: Branden Reid, Ph.D.,
Biomedical Engineer
Gastroenterology Devices
Branch/DRGUD

To: The Record

SUBJECT: NEW DRUG APPLICATION (NDA) 205613
Salix Pharmaceuticals Inc., – Budesonide 2mg rectal foam

BACKGROUND AND SUBMISSION HISTORY

CDER is requesting CDRH/GEDB's advice as to whether or not the “packaging” of the rectal foam qualifies as a device thereby making this a combination product. CDER also requests CDRH/GEDB's advice as to whether or not additional studies are needed to evaluate the safety and effectiveness of this product to deliver the prescribed dose.

After discussion with Office of Combination Products (OCP) (Patricia Love and Angela Krueger) and CDER (Marie Kowblansky), we have determined that the canister should be classified as a device and not “packaging”.

Marie Kowblansky (CDER) stated in an email:

“Each multi-dose canister delivers fourteen 1.35-mL doses of foam product (equivalent to 2 mg budesonide per dose) and is provided with 14 single-use, disposable rectal applicators.

[REDACTED] (b) (4)
[REDACTED] (u) (4)
The metered dose of the foam is delivered by a disposable, [REDACTED] (u) (4), dose-metering, multi-dose canister.”

Therefore as previously mentioned, due to the specific delivery dose of the drug, the metering device is not just packaging.

In regards to GEDB's evaluation of the meter dosage we have never reviewed a device as such before. As a result, I spoke to Nayan Patel (Anesthesiology/ODE) and Sugato De (Respiratory/ODE) who have reviewed nebulizers. Sugato and Nayan mentioned evaluation techniques such as cascade impaction, which can measure particle sizes. Since the particle size may not matter in this case, mass spectroscopy would probably be sufficient. However, we first need to determine how well the drug gets into solution. That needs to be determined prior to evaluating the metered dosage.

In an internal meeting on February 28, 2014, Marie Kowblansky (CDER) stated that her team will evaluate the metered dosage and leachability studies. GEDB will evaluate the biocompatibility of the rectal applicator.

INDICATIONS AND USAGE

Budesonide rectal foam is indicated for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

DEVICE DESCRIPTION

Budesonide rectal foam (2 mg per metered dose) is supplied as a topical synthetic glucocorticosteroid in a formulation for rectal administration. The dosing regimen is 1 metered dose administered rectally twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks.

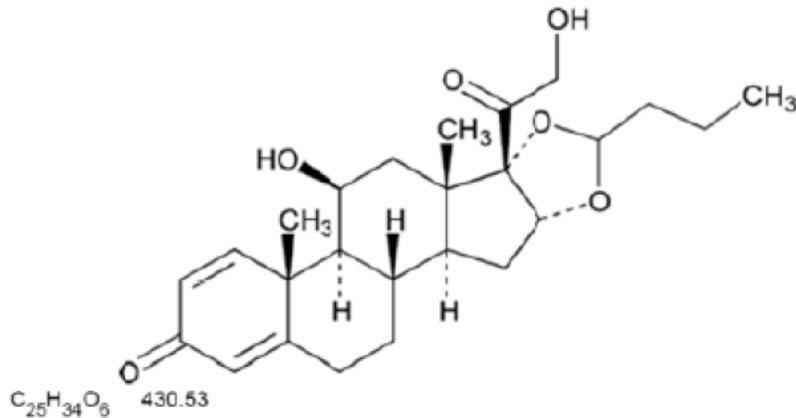
Budesonide rectal foam is formulated as an emulsion which is filled into an aluminum can with an aerosol propellant. It is available in one strength: 2 mg budesonide per metered dose

Budesonide rectal foam contains budesonide, a non-halogenated synthetic glucocorticoid, as the active ingredient. It is a mixture of the two epimers (22R and 22S) differing in the position of an acetal chain. Both epimers are active glucocorticoids applied in a mixture of approximately 1:1.

 (b) (4)

Budesonide is designated chemically as (RS)-11 β , 16 α , 17,21 tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. The empirical formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.5. Its structural formula is:

Figure 1: Structural formula of Budesonide



Inactive ingredients: cetyl alcohol, citric acid monohydrate, edetate disodium, emulsifying wax, polyoxyl (10) stearyl ether, propylene glycol, and purified water.

Propellant: n-butane, isobutane, and propane.

Container Closure System:

The primary container closure system for the drug product is comprised of a 54-mL, white, aluminum (b) (4) canister (b) (4) (b) (4) (b) (4), fitted with a 1-inch metering valve consisting of a (b) (4) valve body and stem affixed with a 1.35-mL metering head. A plastic safety tab that prevents accidental actuation is attached to a foam shield and must be removed prior to use. The canister only delivers a dose when it is held inverted. Once activated, the valve opens and the metering head dome fills with a single dose of the drug product emulsion and propellant mixture. The foam is expelled once the metering head is released.

Each Budesonide 2 mg Rectal Foam canister will be provided in a cardboard carton containing 2 trays of 7 single-use, disposable, white, polyvinyl chloride (PVC) rectal applicators (for a total of 14 applicators). Each applicator is coated with paraffin, (b) (4). Plastic bags are included in the secondary packaging for safe and hygienic disposal of the used applicators.

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Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Carcinogenicity studies with budesonide were conducted in rats and mice. In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 µg/kg. In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 µg/kg and above. No tumorigenicity was seen in female rats at oral doses up to 50 µg/kg.

In an additional 2-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 µg/kg. However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 µg/kg. The concurrent reference glucocorticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 µg/kg.

Mutagenesis

Budesonide showed no evidence of mutagenic potential in the Ames test, the mouse lymphoma cell forward gene mutation (TK+/-) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocyte UDS test or the mouse micronucleus test.

Impairment of Fertility

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 µg/kg

(b) (4)
(b) (4). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 µg/kg (b) (4) and above. No such effects were noted at 5 µg/kg.

Reviewer Comment: *We should ask CDER if leachability studies are needed to evaluate the interaction of the canister/device and foam.*

QUESTIONS TO CDER:

1. Budesonide 2mg rectal foam appears to be a similar device as the Cortifoam (Hydrocortisone Acetate) Rectal Metered Aerosol (approved July 8, 2002). Have you examined this submission or other similar products to compare in the review of Budesonide?

CDER's response: *CDER is looking into other similar products.*

2. The sponsor provided pharmacokinetics of the Budesonide 2mg rectal foam. Does their data support evidence of sufficient drug distribution throughout the foam to CDER's standards?

CDER's response: CDER will evaluate the sponsor's pharmacokinetics data.

3. Should the sponsor be asked to address the pressure effects of the aerosol components on the anus? What is a reasonable amount of force that can be applied to the anus?

CDER's response: CDER is looking into other similar products for comparison.

4. Should the sponsor be asked to provide the proximal distribution of the foam?

CDER's response: CDER will evaluate the sponsor's proximal distribution of foam data.

5. Should the sponsor be asked to provide leachability studies to evaluate the interaction of the canister/device and foam.

CDER's response: CDER will evaluate the sponsor's leachability studies.

6. How well does the drug get into solution? That needs to be determined prior to evaluating the metered dosage.

CDER's response: Tarun Mehta (CDER/CMC) stated that his team will be evaluating how well the drug gets into solution.

DEFICIENCIES TO THE SPONSOR

1. You refer to your canister as "packaging". It has been determined that the canister should be classified as a device and not "packaging".
2. According to the FDA Blue Book Memorandum #G95-1, entitled Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.", your rectal applicator is considered limited surface contacting. We recommend cytotoxicity, sensitization, and irritation / intracutaneous reactivity tests per FDA's recognized standards to 2-117: AAMI / ANSI / ISO 10993-3:2003/(R) 2009.
3. You provide instructions for use of the rectal foam. The last instruction states, (b) (4)
" We recommend mentioning emptying the bowels before application as an initial instruction for clarity. -
4. In your instructions for use of the rectal foam you state, (b) (4)
Please elaborate on how the drug delivery will be affected by the speed of release. Please explain how you have

incorporated risk mitigations to address these issues.

5. You provide diagrams of the device components in your submission; however, you have not provided measurements and units. Please provide measurements and units of each device component.

RECOMMENDATION

The sponsor should be asked to address the above deficiencies.

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Chief Sign-Off	

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/s/

KELLY D RICHARDS
08/12/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: June 23, 2014
Requesting Office or Division: Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number: NDA 205613
Product Name and Strength: Uceris (Budesonide) Rectal Foam, 2 mg
Product Type: Drug-Device Combination Product
Rx or OTC: Rx
Applicant/Sponsor Name: Salix Pharmaceuticals INC
Submission Date: November 15, 2013
OSE RCM #: 2014-232
DMEPA Primary Reviewer: Matthew Barlow RN, BSN
DMEPA Associate Director: Lubna Merchant, PharmD, M.S

1 REASON FOR REVIEW

As part of their evaluation for NDA 205613, DGIEP requested we evaluate the prescribing information, container label, carton labeling along with the instructions for use for NDA 205613 Uceris (Budesonide) 2 mg Rectal Foam for areas of vulnerability that may lead to medication errors. .

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing a new formulation of their already marketed 9 mg tablet dosage form. The proposed product will have the same indication as the tablet, but is a rectal foam that administers 2 mg per actuation. We performed a risk assessment of the proposed Full Prescribing Information, Patient Instructions for Use, Labels and Labeling to identify deficiencies that may lead to medication errors.

We note that the route of administration is not prominently displayed and may be overlooked, and the net quantity is not noted on the labels. Additionally, the statement "shake well," is noted on the side panels of the label, which could be overlooked. We provide recommendations in Section 4.1 for the label and labeling to improve readability and ensure safe use of the product.

The Applicant has proposed the strength presentation as 2 mg; however, the appropriate strength presentation (per ONDQA) should be 2 mg/actuation.

We also identified areas of improvement for the Instructions for Use (IFU). Our recommendations for the IFU will be incorporated in the DMPP review.

4 CONCLUSION & RECOMMENDATIONS

We recommend that Salix Pharmaceuticals Inc. increase the readability and prominence of important information in the proposed labeling to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE APPLICANT

A. Carton Labeling

1. As currently presented, the dosage form is not present next to the established name. The established name presentation should include the active ingredient followed by the dosage form. Relocate the dosage form “Rectal foam” immediately following the active ingredient as shown below. Additionally, revise the strength presentation to 2 mg/actuation

“Uceris

(budesonide) Rectal Foam

2 mg/actuation”

2. The established name is presented (b) (4) against a dark blue background which decreases the readability and prominence. Revise the presentation of the established name to a white font to commensurate in prominence with the proprietary name per 21 CFR 201.10(g) (2).
3. Consider revising the presentation of the proprietary name from all uppercase (i.e. UCERIS) to title case where the letter ‘U’ is capitalized (i.e. Uceris) to improve readability of the name.
4. List the net quantity statement on the bottom left of the principal display panel.
5. Revise the statement “please see complete prescribing...” on the side panel to the following; “For the usual dosage please see the enclosed prescribing information”
6. Relocate the statement “For Rectal Use Only-...” to the principal display panel (PDP) below the strength presentation.

7. Relocate the statement “shake well before using” to the principal display panel below the “For Rectal Use Only-...” to increase the prominence of this statement so this information does not get overlooked.

B. Container Label

1. See A1 – A5
2. We recommend you bold and relocate the statements “For rectal administration only, as directed by physician,” and “Shake well before using,” to the PDP below the strength presentation. The storage information can be moved to the side panel to accommodate the above statements

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Uceris that Salix Pharmaceuticals INC submitted on February 18, 2014.

Table 2. Relevant Product Information for Uceris	
Active Ingredient	Budesonide
Indication	Induction of remission in patients with active, mild to moderate ulcerative colitis extending up to 40cm from the anal verge.
Route of Administration	Rectal
Dosage Form	Rectal Foam
Strength	2 mg
Dose and Frequency	1 metered dose (2 mg) administered two times a day for two weeks, followed by 1 metered dose administered once a day for four weeks.
How Supplied	Box with 1 aerosol container (will deliver 14 metered doses total) and 14 applicators.
Storage	Store at room temperature between 68°F and 77°F.
Container Closure	The primary container closure system for the drug product is comprised of a 54-mL, white, aluminum ^{(b) (4)} canister ^{(b) (4)} , fitted with a 1-inch metering valve consisting of a ^{(b) (4)} valve body and stem affixed with a 1.35-mL metering head. A plastic safety tab that prevents accidental actuation is attached to a foam shield and must be removed prior to use.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 14, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Table 3: FAERS Search Strategy	
Date Range	Searched up to March 14, 2014
Drug Names	Uceris [product name]
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issues NEC (HLT) Product Labeling Issue (HLT) Product Packaging Issues (HLT)

B.2 Results

Our search identified no cases.

B.3 List of FAERS Case Numbers

N/A

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

We reviewed the following Uceris labels and labeling submitted by Salix Pharmaceuticals INC on February 18, 2014.

- Container label
- Carton labeling
- Instructions for Use (no image included)
- Medication Guide (no image included)

C.2 Label and Labeling Images



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

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/s/

MATTHEW J BARLOW
06/23/2014

LUBNA A MERCHANT
06/24/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

*** This document contains confidential information that cannot be released to the public***

DATE: June 13, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Kelly Richards, Regulator Project Manager, CDER/OND/ODEIII/DGIEP

SUBJECT: **NDA 205613**
Applicant: Salix Pharmaceuticals, Inc
Drug: Budesonide 2 mg
Device: Rectal foam canister
Intended Use: treatment of ulcerative (b) (4)
CDRH CTS Tracking: ICC1400105

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA 205613
Applicant: Salix Pharmaceuticals, Inc
Drug: Budesonide 2 mg
Device: Rectal foam canister
Intended Use: treatment of ulcerative proctitis

CDRH Human Factors Involvement History

- 2/6/2014 – CDRH HFPMET was requested to review the NDA. At the time of the initial review, the NDA did not provide any information on use-related risk analysis and human factors evaluation.
- 2/28/2014 – CDRH HFPMET provided deficiencies to project manager (Kevin Burgin) requesting for the necessary information to complete the review.
- 6/10/2014 – Project manager (Kelly Richards) provided the Sponsor's response to the requested information.
- 6/13/2014 – CDRH HFPMET participated in an internal meeting to report that we are in agreement that a human factors validation study is not necessary for this product based on the risk analysis that the Sponsor provided.
- 6/13/2014 – CDRH HFPMET provided final review recommendation to project manager.

Overview and Recommendation

The Division of Gastroenterology, and Inborn Errors Products, Office of New Drugs, Center for Drugs Evaluation and Research requested a consultative review from CDRH Human Factors Premarket Evaluation Team on the rectal form device (canister) to deliver budesonide intended to treat ulcerative (b) (4)

The original submission did not include any information relating to a use-related risk analysis or human factors evaluation. As a result, an information request was issued requesting Salix Pharmaceuticals, the Sponsor, to provide a comprehensive use-related risk analysis and a justification for whether a human factors validation study is needed. The request is provided here for ease of review:

The submission does not include a systematic evaluation of use-related risk, a determination of the necessity of human factors (HF) validation and, if necessary, how you would undertake the human factors validation. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. This risk analysis of user tasks should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. You should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-

mitigation strategies. Provide a comprehensive analysis of use-related risks and a justification for whether an HF/usability validation study is necessary for the proposed product. In addition, provide a discussion on how you have addressed potential difficulty that the user may experience when administering the product in a specific position.

The Sponsor provided the response via a Quality Information Amendment. The Sponsor reported that performed a systematic evaluation of use-related risk for budesonide 2 mg rectal foam in accordance with the 2011 draft guidance, Applying Human Factors and Usability Engineering to Optimize Medical Device Design. A task prioritization chart, showing the potential clinical consequence and risk prioritization for each task involved with delivering the drug, is presented in Table 1 of the response.

The risk analysis did not identify any use errors or major or serious risks that could lead to negative clinical consequence while using the canister to administer budesonide 2 mg rectal foam. The Sponsor concluded that taken into consideration the risk analysis and the additional data generated during two pivotal Phase 3 clinical studies in which the drug was delivered with this device in accordance with the instructions for use, a human factors validation is not necessary.

At the 6/13/2014 internal meeting, there were some concerns associated with product performance i.e. delivery of the full 100% drug after first actuation. There were other concerns associated with the patient needing to hold the device in place for 10 seconds before withdrawing the canister. At this meeting, CDRH HFPMET iterated that the Sponsor has performed a use-related risk analysis and did not identify any safety concerns associated with users not holding it in place for 10 seconds. The issues associated with product performance would be addressed through engineering and CMC review.

In conclusion, this consultant concurs with the Sponsor's conclusion, and does not believe that CDRH HFPMET needs to review a human factors validation study for this submission.

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/s/

KELLY D RICHARDS

06/19/2014

Checked in for QuynhNhu Nguyen, Combination Products Human Factors Specialist

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

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205613

Application Type: New NDA

Name of Drug/Dosage Form: budesonide rectal foam, 2 mg

Applicant: Salix Pharmaceuticals, Inc

Receipt Date: November 15, 2013

Goal Date: September 15, 2014

1. Regulatory History and Applicant's Main Proposals

NDA 205613 is submitted to support marketing of Budesonide 2 mg Rectal Foam for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 18, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

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

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

➤ **For the Filing Period:**

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

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

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

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

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

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

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

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

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

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
***Comment:** In the TOC, all subheadings should be indented.*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- NO** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
***Comment:** Section 9.0 is missing. An asterisk is required.*

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment: *The word "See" should be in italics.*

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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
01/28/2014

RICHARD W ISHIHARA
01/28/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 205613 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: Budesonide Dosage Form: Aerosolized Foam Strengths: 2 mg		
Applicant: Salix Pharmaceuticals, Inc Agent for Applicant (if applicable):		
Date of Application: November 15, 2013 Date of Receipt: November 15, 2013 Date clock started after UN:		
PDUFA Goal Date: September 15, 2014		Action Goal Date (if different):
Filing Date: January 14, 2014		Date of Filing Meeting: January 09, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 104725				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

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

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pending contact to PeRC.

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

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	OSE has requested an update on the prop. Name submission.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT-IRT, CDRH, PMHS

4

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

<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 07/23/213	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 01/09/2014

BLA/NDA/Supp #: 205613

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: budesonide

DOSAGE FORM/STRENGTH: Aerosolized Foam/2 MG

APPLICANT: Salix Pharmaceuticals, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

Indicated for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

BACKGROUND:

Salix Pharmaceuticals, Inc has been developing a US version of budesonide rectal foam from Europe under IND 104725. Upon completion of two Phase 3 studies, the Sponsor met with the Division for a Pre-NDA meeting in July 2013. The Sponsor subsequently submitted NDA 205613 to support marketing of Budesonide 2 mg Rectal Foam for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kelly Richards	Y
	CPMS/TL:	Richard Ishihara	Y
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		Y
Clinical	Reviewer:	Zana Marks Handy	Y
	TL:	Anil Rajpal	Y

Clinical Pharmacology	Reviewer:	Lucy Fang	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:	Shahla Farr	Y
	TL:	Freda Cooner	Y
Product Quality (CMC)	Reviewer:	Terun Mehta	Y
	TL:	Marie Kowblansky	Y
OSE/DMEPA (proprietary name)	Reviewer:	Lisa Khosla	N
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	TBD	N
	TL:	TBD	N

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	Susan Leibenhaut	Y
Other reviewers	Pharmacometrics/Nitin Mehrotra		N

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: N/A</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: N/A</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments: Not an NME</p> <p>If no, for an NME NDA or original BLA , include the reason. For example:</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments: N/A</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments: N/A</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments: N/A</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: N/A</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: N/A</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: N/A</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: N/A</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: N/A</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: N/A</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>CMC Labeling Review</u></p> <p>Comments: N/A</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Donna Griebel</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments: See Attached Review Reference Sheet</p>	

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

Receipt Date: 15 Nov 2013
PDUFA Goal Date: 15 Sep 2014

Signatory Authority: Donna Griebel
CDTL: Anil Rajpal

Reviewers:

Clinical TL	Anil Rajpal
Clinical Reviewer	Zana Marks
Clinical Pharmacology TL	Sue Chih Lee
Clinical Pharmacology	Lucy Fang
Pharmacometrics TL	Nitin Mehrotra
Pharmacometrics	TBD
Product Quality TL	Marie Kowblansky
Product Quality Reviewer	Tarun Mehta
Biometrics TL	Freda Cooner
Biometrics Reviewer	Shahla Farr
Nonclinical TL	Sushanta Chakder
Nonclinical Reviewer	Dinesh Gautam

Links:

EDR:	\\CDSESUB1\evsprod\NDA205613\205613.enx
eRoom:	http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_3fde1

Goals:	
Filing Determination Date	14 Jan
Primary Reviews Due	11 Aug
Secondary Reviews Due	18 Aug
Labeling to Sponsor	18 Aug
CDTL Review Due	25 Aug
DD Review Due	15 Sep

Consultants:

OSE RPM	Phong Do
OPDP (DDMAC)	Adevale Adeleye
DMEPA TL	Lubna Merchant
DMEPA Reviewer	Lisa Khosla
Patient Labeling TL	<i>TBD</i>
Patient Labeling Reviewer	<i>TBD</i>
DMEPA Prop Name	Lisa Khosla
OSI TL	Susan Leibenhaut
PMHS MO	Erica Radden
PMHS RPM	Millie Wright

Meeting Conference Info:

Phone – (b) (4)
Web – <https://collaboration.fda.gov/nda205613>

Milestone Meetings:

Meeting	Date
BIMO Site Selection Meeting	TBD
Filing Meeting	Jan 09
Planning Meeting	Jan 14
Mid Cycle Meeting	APR
Mid Cycle Communication with Applicant	APR
Labeling Planning Meeting	MAY
PeRC	JUL
Wrap Up Meeting	AUG

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
01/28/2014

RICHARD W ISHIHARA
01/28/2014