

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211929Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: May 30, 2019

Requesting Office or Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Application Type and Number: NDA 211929

Product Name and Strength: Ortikos (budesonide) capsule, 6 mg and 9 mg

Applicant/Sponsor Name: Sun Pharma Global FZE

FDA Received Date: May 21, 2019

OSE RCM #: 2018-669-3

DMEPA Safety Evaluator: Sherly Abraham, R Ph

DMEPA Team Leader (Acting): Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container labels for Ortikos (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

On May 21, 2019, the Applicant submitted revised container labels for Ortikos which did not implement our recommendation to revise the expiration date format as outlined in our Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act: Questions and Answers FDA (available at <https://www.fda.gov/media/116304/download>). This guidance states that the human-readable expiration date on the drug package label include a year, month, and non-zero day. Per the guidance, we recommend that the expiration date appear in YYYY-MM-DD format (if only numerical characters are used) or in YYYY-MMM-DD (if alphabetical characters are used to represent the month). If there are space limitations on the drug package, the human-

^aAbraham, S. Label and Labeling Review for Ortikos (NDA 211929). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 May 21. RCM No.:2018-669-2.

readable text may include only a year and month, to be expressed as: YYYY-MM (if only numerical characters) are used or YYYY-MMM (if alphabetical characters are used to represent the month).

On May 27, 2019, the Applicant submitted their rationale as to why they would like to maintain the format of their proposed expiration date of MM/YYYY:

"...we proposed expiration date format as "MM/YYYY" versus FDA's proposed format "YYYY-MM" because, the manufacturing site is following "MM/YYYY" format for all the products manufactured at this site. This format (MM/YYYY) has been accepted for many approved products by the FDA. Changing format only for this product (NDA 211929) would be difficult and may create confusion at the manufacturing site. Also, providing expiration date in "MM/YYYY" would not create any medication error and therefore, we request FDA to consider our proposal for using expiration date format as "MM/YYYY". Please confirm if the proposed expiration date format is acceptable to the FDA."

3 CONCLUSION

We acknowledge the Applicant's rationale received on May 27, 2019 and do not have safety concerns with their proposed expiration date format. However, we note that the United States Pharmacopeia (USP) has proposed a standard for formatting expiration dates that aligns with the format stated in the Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act: Questions and Answers FDA. Therefore, Sun Pharma should consider adopting the recommended format of FDA and USP for all expiration dates in their entire product line.

4 RECOMMENDATIONS FOR SUN PHARMA GLOBAL FZE

We recommend the following be conveyed to the Applicant prior to approval of this NDA:

We find your proposed expiration date format acceptable from a safety perspective. We note that the draft guidance "Product Identifiers Under the Drug Supply Chain Security Act: Questions and Answers" (available at <https://www.fda.gov/media/116304/download>) is not binding on the FDA or the public; however it reflects the Agency's current thinking on what expiration date formats are optimal.

Specifically, where there are no space limitations, we recommend YYYY-MM-DD if using only numeric characters, or YYYY-MMM-DD if using alphanumeric characters. Where there are space limitations, we recommend YYYY-MM if using only numeric characters or YYYY-MMM if using alphanumeric characters.

However, please note that the United States Pharmacopeia (USP) has proposed a standard for formatting expiration dates that aligns with the format stated in the Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act: Questions and Answers FDA. Therefore, we recommend that you consider adopting the recommended format of FDA and USP for all expiration dates in your entire product line.

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/s/

SHERLY ABRAHAM
05/31/2019 09:06:17 AM

IDALIA E RYCHLIK
05/31/2019 10:27:45 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: May 21, 2019
Requesting Office or Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number: NDA 211929
Product Name and Strength: Ortikos (budesonide) capsule, 6 mg and 9 mg
Applicant/Sponsor Name: Sun Pharma Global FZE
FDA Received Date: May 21, 2019
OSE RCM #: 2018-669-2
DMEPA Safety Evaluator: Sherly Abraham, R Ph
DMEPA Team Leader (Acting): Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised prescribing information and container labels for Ortikos (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendation that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant submitted revised container labels for Ortikos received on May 21, 2019. We find the container labels unacceptable from a medication error perspective. The expiration date is not in the requested specified format.

3 RECOMMENDATIONS FOR SUN PHARMA GLOBAL FZE

We recommend the following be implemented prior to approval of this NDA:

^aAbraham, S. Label and Labeling Review for Ortikos (NDA 211929). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 May 14. RCM No.:2018-669-1.

Table 1. Identified Issues and Recommendations for Sun Pharma Global FZE (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The format of the expiration date is incorrect.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Revise the expiration date to the correct format. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

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/s/

SHERLY ABRAHAM
05/21/2019 03:26:12 PM

IDALIA E RYCHLIK
05/21/2019 03:28:06 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: May 14, 2019
Requesting Office or Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number: NDA 211929
Product Name and Strength: Ortikos (budesonide) capsule, 6 mg and 9 mg
Applicant/Sponsor Name: Sun Pharma Global FZE
FDA Received Date: April 22, 2019
OSE RCM #: 2018-669-1
DMEPA Safety Evaluator: Sherly Abraham, R Ph
DMEPA Team Leader (Acting): Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised prescribing information and container labels for Ortikos (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant submitted revised prescribing information and container labels for Ortikos received on April 22, 2019. We find the prescribing information acceptable; however, container labels are unacceptable from a medication error perspective. The expiration date statement is denoted by a placeholder instead of the specified format.

3 RECOMMENDATIONS FOR SUN PHARMA GLOBAL FZE

We recommend the following be implemented prior to approval of this NDA:

^aAbraham, S. Label and Labeling Review for Ortikos (NDA 211929). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 19. RCM No.:2018-669.

Table 1. Identified Issues and Recommendations for Sun Pharma Global FZE (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The expiration date statement is denoted by a placeholder (XXXXXXX).	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Change the expiration date to the correct format. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

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/s/

SHERLY ABRAHAM
05/14/2019 11:22:55 AM

IDALIA E RYCHLIK
05/14/2019 12:17:52 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: January 28, 2019
Requesting Office or Division: Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number: NDA 211929
Product Name and Strength: budesonide capsule, 6 mg and 9 mg
Submission date: January 25, 2019
Applicant/Sponsor Name: Sun Pharma Global FZE
OSE RCM #: 2018-669-1
DMEPA Primary Reviewer: Sherly Abraham, R.Ph.
DMEPA Team Leader: Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the container labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review^a.

2 CONCLUSION

We find the revised container labels acceptable from medication error perspective and have no further recommendations at this time.

^aAbraham, S. Label and Labeling Review for budesonide (NDA 211929). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Oct 19. RCM No.: 2018-669.

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/s/

SHERLY ABRAHAM
01/28/2019 01:32:57 PM

SARAH K VEE
01/28/2019 01:34:48 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
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
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, M.D., Pediatric Team Leader
John J. Alexander, M.D., M.P.H., Deputy Director
DPMH, ODE IV, OND

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

Drug: Budesonide capsules

Application Number: NDA 211929

Sponsor: Sun Pharma Global FZE

Proposed Indications:

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older
- Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults

Proposed Dosage Form: 6 mg and 9 mg capsules

Proposed Route of Administration: For oral administration

Proposed Dosing Regimen: *Treatment of mild to moderate active Crohn's disease:*

- Adults: 9 mg once daily for up to 8 weeks; repeat 8 week treatment courses for recurring episodes of active disease.
- Pediatric patients 8 to 17 years who weigh more than 25 kg: 9 mg once daily for up to 8 weeks, followed by 6 mg once daily in the morning for 2 weeks.

Maintenance of clinical remission of mild to moderate Crohn's disease:

- Adults: 6 mg once daily for up to 3 months; taper to complete cessation after 3 months. Continued treatment for more than 3 months has not been shown to provide substantial clinical benefit.

Consult Request: DGIEP consulted DPMH on April 16, 2018 to provide assistance with labeling recommendations for pediatric use.

Materials Reviewed:

- DPMH consult request (dated April 16, 2018 in DARRTS)
- Applicant's proposed labeling for budesonide capsules, NDA 211929 (submitted June 25, 2018)
- Current Entocort EC (budesonide) capsules labeling, NDA 021324 (November 12, 2018 in FDALabel)
- DPMH's prior review for Entocort (budesonide) capsules, NDA 021324 (dated April 6, 2016 in DARRTS)

I. Regulatory History of this Application

Ortikos (budesonide) 6 and 9 mg capsule is an oral corticosteroid formulated for extended release into the intestinal lumen. Oral budesonide was originally approved on October 2, 2001 under the proprietary name Entocort EC (3 mg capsules) for treatment (induction of remission) of mild to moderate active Crohn's disease (CD) involving the ileum and/or the ascending colon in adults. Entocort EC was then approved on April 29, 2005 for the maintenance of remission of mild to moderate CD for up to 3 months in adults.

On March 30, 2018, Sun Pharma Global FZE submitted a new drug application (NDA) for budesonide 6 and 9 mg capsules under the 505(b)(2) pathway using Entocort as the listed drug and plans to support approval based on a demonstration of bioequivalence to Entocort EC. Sun Pharma Global proposes to seek the same indications and dosing

regimen approved for Entocort EC. However, Sun Pharma Global has developed higher strength capsules that would reduce the total number of capsules taken daily (i.e., three 3 mg capsules [totaling a 9 mg dose] of Entocort compared to one 9 mg capsule of Ortikos or two 3 mg capsules of Entocort [totaling a 6 mg dose] compared to one 6 mg capsule of Ortikos).

Upon approval of Entocort EC for each respective indication, DGIEP issued the following post-marketing requirements (PMRs) under the Pediatric Research Equity Act (PREA):

- a deferred pediatric study for the treatment of mild to moderate active CD involving the ileum and/or ascending colon in pediatric patients ages 5 to 17 years
- a deferred study under PREA for the maintenance of remission in CD in pediatric patients ages birth to 17 years

The Entocort application holder submitted an efficacy supplement to fulfill these two PREA PMRs on June 30, 2015. The Agency determined that the data were only sufficient to support an indication for treatment (induction of remission) in patients 8 years and older weighing more than 25 kg, (b) (4)

(b) (4)
(b) (4) Furthermore, the Agency concluded that the application holder showed due diligence to complete studies (b) (4) and deemed both PREA PMRs fulfilled. Accordingly, on April 29, 2016, labeling was updated to extend the treatment indication down to patients 8 years and older and include a description of the maintenance trial in the Pediatric Use subsection.

Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Sun Pharma is seeking approval of a different dosage strength (6 mg and 9 mg oral capsules) of budesonide as opposed to the 3 mg oral capsules approved for Entocort but otherwise proposes the same indications and dosing regimen that are approved for Entocort. Because this NDA does not include any of these triggers, PREA does not apply. DGIEP has requested DPMH-Pediatric Team's assistance with the review of this application and labeling for pediatric use.

II. DPMH Review of Pediatric Use Labeling:

This DPMH-Pediatric Team labeling review will focus on edits to Subsection 8.4 (Pediatric Use). Additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text.

Applicant's Proposed Labeling:

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----DOSAGE AND ADMINISTRATION-----

Recommended Dosage:

Mild to moderate active Crohn's disease (2.2):

- Adults: 9 mg once daily for up to 8 weeks; repeat 8 week treatment courses recurring episodes of active disease.
- Pediatric patients 8 to 17 years who weigh more than 25 kg: 9 mg once daily for up to 8 weeks, followed by 6 mg once daily in the morning for 2 weeks.

Reviewer Comment: We recommend changing [REDACTED] ^{(b) (4)} to "pediatric patients" throughout the labeling.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

8.4 Pediatric Use

The safety and effectiveness of [REDACTED] ^{(b) (4)} ORTIKOS have been established in pediatric patients 8 to 17 years of age who weigh more than 25 kg for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. Use of [REDACTED] ^{(b) (4)} ORTIKOS in this age group is supported by evidence from adequate and well controlled studies of oral budesonide in adults, with additional data from 2 clinical studies in 149 pediatric patients treated up to 8 weeks and one pharmacokinetic study in 8 pediatric patients [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.1)*].

The observed safety profile of oral budesonide in pediatric patients is consistent with its known safety profile in adults and no new safety concerns were identified [see *Adverse Reactions (6.1)*].

(b) (4)

The safety and effectiveness of (b) (4) ORTIKOS have not been established in pediatric patients less than 8 years of age for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

The safety and effectiveness of (b) (4) ORTIKOS have not been established in pediatric patients for the maintenance of clinical remission of mild to moderate Crohn's disease. An open-label study to evaluate the safety and tolerability of oral budesonide as maintenance treatment in pediatric patients aged 5 to 17 years was conducted and did not establish the safety and efficacy of maintenance of clinical remission.

Systemic corticosteroids, including (b) (4) ORTIKOS, may cause a reduction of growth velocity in pediatric patients. Pediatric patients with Crohn's disease have a 17% higher mean systemic exposure and cortisol suppression than adults with Crohn's disease [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)].

Reviewer comment: Because the applicant is seeking approval for the proposed product, Ortikos, based on the data and findings for the listed drug, Entocort, and proposes the same indications and dosing regimen as Entocort, labeling should be similar. However, labeling should clarify that safety and effectiveness have been determined for this specific oral budesonide product by including the proprietary name where appropriate. Additionally, we agree with DGIEP's proposed labeling which describes that clinical studies supporting the approval of this budesonide product were conducted using another oral budesonide product (i.e., Entocort EC) at the beginning of subsection 6.1 (Clinical Trials Experience) and section 14 (Clinical Trials).

Of note, when compared to the size of the Entocort capsule (i.e., size 1 [19.274 mm], which is currently approved for the proposed pediatric population (i.e., patients 8 years and older), the proposed Ortikos capsules is essentially the same or smaller (i.e., 9 mg capsule is also size 1 [19.580 mm] and the 6 mg capsule is size 2 [18.000 mm]). Although, in general, patients 6 years of age and older may be able to swallow a tablet/capsule¹, recent guidance from the European Medicines Agency² provides additional recommendations on the size of tablet/capsule a pediatric patient can reasonably swallow. The guideline would characterize this capsule as large and

¹ Meltzer EO, Welch MJ, Ostrom NK. Pill swallowing ability and training in children 6 to 11 years of age. *Clin Pediatr.* 2006;45:725-733.

² Guideline on Pharmaceutical Development of Medicines for Paediatric Use, January 3, 2013.

recommend use in patients 12 years and older. However, the guideline also notes that patients with chronic diseases may be trained to take tablets/capsules of a larger size than normally considered acceptable. Therefore, given the prior approval of Entocort, a similarly sized or larger capsule, in this population and the proposed duration of treatment (up to 10 weeks) for a chronic condition in which pediatric patients may be trained to take such capsules, the Ortikos capsules appears to be appropriate for the proposed population.

III. DPMH Actions and Labeling Recommendations:

DPMH reviewed the applicant's draft labeling and provided recommended labeling for the pediatric population in accordance with 21 CFR 201.57(c)(9)(iv). DPMH's 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.

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/s/

ERICA D RADDEN
01/25/2019 10:17:12 AM

MONA K KHURANA
01/25/2019 10:31:31 AM

**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: January 18, 2019

To: Dragos Roman, MD
Acting Director
Division of Gastroenterology and Inborn Error Products (DGIEP)

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

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
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): ORTIKOS (budesonide)

Dosage Form and Route: extended-release capsules, for oral use

Application Type/Number: NDA 211929

Applicant: Sun Pharma Global FZE

1 INTRODUCTION

On March 28, 2018, Sun Pharma Global FZE submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 211929 for ORTIKOS (budesonide) 6 and 9 mg capsules. The Reference Listed Drug (RLD) is NDA 021324, ENTOCORT EC (budesonide) 3 mg capsules, held by Paddock Laboratories, LLC. Sun has developed 6 mg and 9 mg capsules in order to reduce the number of capsules taken daily. ORTIKOS is indicated for the treatment of mild to moderate Crohn's disease involving the ileum and ascending colon in people 8 years and older and for the maintenance of clinical remission of Crohn's disease involving the ileum and ascending colon for up to 3 months in adults.

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 Error Products (DGIEP) on April 16, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ORTIKOS (budesonide) extended release capsules.

2 MATERIAL REVIEWED

- Draft ORTIKOS (budesonide) PPI received on March 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 14, 2019.
- Draft ORTIKOS (budesonide) Prescribing Information (PI) received on March 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 14, 2019.

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.

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 reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is 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 is 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.

Please let us know if you have any questions.

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MEETA N PATEL
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MARCIA B WILLIAMS
01/18/2019 11:41:09 AM

LASHAWN M GRIFFITHS
01/18/2019 12:11:35 PM

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

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

Memorandum

Date: January 16, 2019

To: Lawrence Allan, Regulatory Project Manager, (DGIEP)
Joette Meyer, Associate Director for Labeling, (DGIEP)

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

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Budesonide capsules, for oral use

NDA: 211929

In response to DGIEP's consult request dated April 16, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Budesonide.

PI and PPI: OPDP has no comments on the proposed draft PI, received by electronic mail from DGIEP on January 14, 2019.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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

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

Memorandum

Date: January 16, 2019

To: Lawrence Allan, Regulatory Project Manager, (DGIEP)
Joette Meyer, Associate Director for Labeling, (DGIEP)

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

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Budesonide capsules, for oral use

NDA: 211929

In response to DGIEP's consult request dated April 16, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Budesonide.

PI and PPI: OPDP has no comments on the proposed draft PI, received by electronic mail from DGIEP on January 14, 2019.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Telephone: 301-796-2200
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Maternal Health Labeling Review

Date: December 18, 2018 **Date consulted:** April 16, 2018

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health,
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health,
Division of Pediatric and Maternal Health

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

Drug: Budesonide Capsules

Class: Synthetic Corticosteroids

NDA: 211929

Applicant: Sun Pharma Global FZE

Subject: Pregnancy and Lactation Labeling Rule (PLLR)

Indication: For: the treatment of:

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older.
- Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults.

Materials Reviewed:

- March 30, 2018, initial submission for Budesonide, NDA 211929
- May 30, 2018, Applicant's Summary of Literature Search on the Use of Budesonide

During Pregnancy, Lactation, and on the Drug's Potential Effects on Fertility and labeling in PLLR as a response to Division's request of May 3, 2018

- April 16, 2018, DGIEP's consult request to DPMH for Budesonide labeling review, DARRTS Reference ID: 4249310

Consult Question: Assist with Pregnancy and Lactation Labeling Rule (PLLR).

INTRODUCTION

On March 30, 2018, the applicant, Sun Pharma Global (SPG), submitted an original New Drug Application (NDA 211929) for Budesonide Capsules, 6 mg and 9 mg under the 505(b)(2) pathway with reliance on publicly available information. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on April 16, 2018, to provide input for appropriate labeling of the *Pregnancy* and *Lactation* subsections of Budesonide to comply with the PLLR.

BACKGROUND

Regulatory History

SPG relies on the NDA for Entocort[®] EC (budesonide) capsules for oral use (NDA 021324, approved on October 2, 2001), and which is available in a 3-mg strength. SPG developed the new formulation (6 and 9 mg capsules), in order to reduce the number of capsules to be taken daily. [REDACTED] (b) (4)

[REDACTED] (b) (4)

On May 3, 2018, the Division sent a request letter to the applicant to provide support for the PLLR labeling.

On May 30, 2018, the Applicant submitted:

- A review and summary of the available published literature regarding the drug's use in pregnant and breastfeeding women and the effects of the drug on male and female fertility
- A cumulative review and summary of relevant cases reported in applicant's pharmacovigilance database (from the time of product development to present) and
- A revised labeling in PLLR format

Budesonide Drug Characteristics¹

- Budesonide, the active ingredient of budesonide capsules, is a synthetic corticosteroid.
- Molecular weight of 430.5 D
- Half-life of 2 to 3.6 hours after administration of an intravenous dose.
- Mean oral bioavailability of budesonide ranges from 9% to 21% (low) demonstrating a high first-pass elimination of the drug.
- Protein-binding of 85-90%

¹ Entocort existing labeling of October 17, 2017

Current Entocort EC Labeling

The current labeling for Entocort EC (budesonide) states:

HIGHLIGHTS OF PRESCRIBING INFORMATION

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published studies report on the use of budesonide in pregnant women; however, the data are insufficient to inform a drug-associated risk for major birth defects and miscarriage. There are clinical considerations [see *Clinical Considerations*]. In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.5 times or 0.05 times, respectively, the maximum recommended human dose, resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels [see *Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Some published epidemiological studies show an association of adverse pregnancy outcomes in women with Crohn's disease, including preterm birth and low birth weight infants, during periods of increased disease activity (including increased stool frequency and abdominal pain). Pregnant women with Crohn's disease should be counseled regarding the importance of controlling disease.

Fetal/Neonatal adverse reactions

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly.

Data

Animal Data

Budesonide was teratogenic and embryolethal in rabbits and rats. In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis from gestation days 6-15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis). In an embryo-fetal development study in pregnant rabbits dosed during the period of

organogenesis from gestation days 6-18, increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses up to approximately 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis). Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.01 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis).

In a peri- and post-natal development study, rats dosed subcutaneously with budesonide during the period of Day 15 post coitum to Day 21 postpartum, budesonide had no effects on delivery but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures 0.02 times the MRHD (on a mg/m² basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted with oral budesonide, including ENTOCORT EC, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENTOCORT EC and any potential adverse effects on the breastfed infant from ENTOCORT EC, or from the underlying maternal condition.

Data

One published study reports that budesonide is present in human milk following maternal inhalation of budesonide which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.4 and 0.5. Budesonide plasma concentrations were not detected and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide. The recommended daily dose of ENTOCORT EC capsules is higher (up to 9 mg daily) compared with inhaled budesonide (up to 800 mcg daily) given to mothers in the above described study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single- and repeated-dose pharmacokinetic studies) of oral budesonide is approximately (b) (4) which is up to 10 times higher than the (b) (4) for a 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of ENTOCORT EC, budesonide exposure to the nursing child may be up to 10 times higher than that by budesonide inhalation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-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 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.023 times the maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). (b) (4) In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). 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 mcg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise female patients that ENTOCORT EC may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy

REVIEW

For an extensive review of Entocort (budesonide) use in Pregnancy and Lactation the reader is referred to the DPMH consult review by Miriam Dinatale, DO, in DARRTS, Reference ID: 3875179, and dated January 25, 2016.



Review of Literature

Applicant's Review

Few published studies report on the use of budesonide in pregnant women. A literature search in PubMed was conducted identifying clinical information till March 30, 2018. Search terms include: "budesonide OR entocort OR pulmicort OR iberis OR rhinocort OR

budenofalk OR Budeson* OR spiro cort OR symbicort AND cleft * OR embryotox* OR feta* OR malform* OR neural tub* OR pregnancy OR reproduc* OR teratogen* OR teratol* OR motility OR morphology OR sperm* OR defect* OR deform* OR abort* OR perinatal OR prenatal OR postnatal OR embryo OR blastogen*'. For these publications, see Table 1.

Table 1: Publication Reporting on Use of Budesonide in Pregnancy

Author/Year	Study Design	Time of Exposure	Amount/Duration	Outcome/Conclusion												
Silverman et al., 2005 ²	Clinical Trial, a randomized, doubleblind, placebo-controlled. 7241 patients aged 5 to 66 years (2473 females aged 15 to 50 years) with mild-to moderate persistent asthma (Pregnancy was not an exclusion criterion).	Throughout pregnancy	Once daily, budesonide (400 mcg) for adults or placebo via dry powder inhaler in addition to their usual asthma medication for 3 years	313 pregnancies all together reported (196 to Budesonide and 117 to placebo). Healthy children were delivered in 81% and 77% in the budesonide and placebo groups, respectively. Adverse outcomes: Budesonide: 38 (19%) Placebo: 27 (23%) <table style="margin-left: auto; margin-right: auto;"> <tr> <td></td> <td style="text-align: center;">Budesonide</td> <td style="text-align: center;">Placebo</td> </tr> <tr> <td>Miscarriage:</td> <td style="text-align: center;">23 (12%)</td> <td style="text-align: center;">11 (9%)</td> </tr> <tr> <td>Cong. Malfor:</td> <td style="text-align: center;">3 (2%)</td> <td style="text-align: center;">4 (3%)</td> </tr> <tr> <td>Other:</td> <td style="text-align: center;">12 (6%)</td> <td style="text-align: center;">12 (10%)</td> </tr> </table>		Budesonide	Placebo	Miscarriage:	23 (12%)	11 (9%)	Cong. Malfor:	3 (2%)	4 (3%)	Other:	12 (6%)	12 (10%)
	Budesonide	Placebo														
Miscarriage:	23 (12%)	11 (9%)														
Cong. Malfor:	3 (2%)	4 (3%)														
Other:	12 (6%)	12 (10%)														
Beaulieu et al., 2009 ³	Retrospective review of a Case series of 8 mothers with Inflammatory Bowel Disease (IBD) and Crohn's Disease (CD) and their infants	During pregnancy	Budesonide was used at the 6 mg/day dose in 6 patients and 9 mg/day dose in 2 patients. The average treatment duration ranges from 1-8 months.	There were no cases of maternal adrenal suppression, glucose intolerance, ocular side effects, hypertension or fetal congenital abnormalities. They concluded, Budesonide may be a safe option for treatment of Crohn's disease (CD) during pregnancy												
Gluck et al., 2005 ⁴	Review of Clinical and epidemiological studies (5 publications and 3 abstracts). 6600 infants whose mothers were exposed to orally inhaled budesonide.	Either during early pregnancy only or throughout pregnancy	Maternal exposure to orally inhaled or intranasal budesonide (dosage and duration not stated)	Normal gestational age, birth weight, and length, with no increased rate of stillbirths, multiple births, or congenital malformations or cardiovascular defects.												

² Silverman M, Sheffer A, Diaz PV, Lindmark B, Radner F, Broddene M, de Verdier MG, Pedersen S, Pauwels RA. START Investigators Group. Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide. *Ann Allergy Asthma Immunol.* 2005 Dec;95(6):566-70.

³ Beaulieu DB, Ananthakrishnan AN, Issa M, Rosenbaum L, Skaros S, Newcomer JR, Kuhlmann RS, Otterson MF, Emmons J, Knox J, Binion DG. Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. *Inflamm Bowel Dis.* 2009 Jan;15(1):25-8.

⁴ Gluck PA, Gluck JC. A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. *Curr Med Res Opin.* 2005 Jul;21(7):1075-84

Author/Y ear	Study Design	Time of Exposure	Amount/Duration	Outcome/Conclusion
Källén et al., 1999 ⁵	Case study using the Swedish Medical Birth Registry; congenital malformations were studied in 2014 infants.	Mothers had used inhaled budesonide for asthma in early pregnancy.	Not reported	No increase in the general rate of congenital malformations was observed: 3.8% (95% confidence interval [CI] 2.9, 4.6) of the infants had a congenital malformation diagnosed, which is similar to the population rate (3.5%).
Alhussien et al., 2018 ⁶	Review of 3 publications	During pregnancy	Intranasal use of different steroids including budesonide. Dosage was not identified	No significant association with congenital malformations. Budesonide is safe, if used at the recommended therapeutic dose after a proper medical evaluation. Risk/benefit ratio should always be considered before prescribing any intranasal corticosteroid sprays during pregnancy.
Norjavaara et al., 2003 ⁷	Population based study from the Swedish Medical Birth Register, which includes 99% of births in Sweden. During 1995 to 1998, 293,948 newborn infants were identified. Pregnancy outcomes were compared for mothers in Sweden reporting asthma medication usage (2,968 mothers) with those reporting no asthma medication usage.	During early pregnancy	Inhaled budesonide (no dosage is reported)	Infants born to mothers who used budesonide during their pregnancy had normal gestational age, birth weight, and length, with no increased rate of stillbirths or multiple births. The rate of cesarean births was higher among mothers who used asthma medication during their pregnancy. The use of inhaled budesonide in Sweden is not linked with any clinically relevant effects associated with pregnancy outcome.

⁵ Källén B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. *Obstet Gynecol.* 1999 Mar;93(3):392-5.

⁶ Alhussien AH, Alhedaithy RA, Alsaleh SA. Safety of intranasal corticosteroid sprays during pregnancy: an updated review. *Eur Arch Otorhinolaryngol.* 2018 Feb;275(2):325-333.

⁷ Norjavaara E, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2,968 pregnant women exposed to budesonide. *J Allergy Clin Immunol.* 2003 Apr;111(4):736-42.

Author/Year	Study Design	Time of Exposure	Amount/Duration	Outcome/Conclusion
Källén et al., 2003 ⁸	Case control study with cases (cardiovascular defects without known chromosome anomalies) being identified from three Swedish health registers (n=5015) (2230 used budesonide nasal spray) and controls being all infants born in Sweden during the period 1 July 1995-2001 (n=577,730).	Interview on drug exposure in early pregnancy	Budesonide in nasal preparations and use of other drugs.	Some observed associations with any of the medications identified are probably due to confounding from underlying disease, some may be due to multiple testing, and some may be true drug effects. Budesonide used as an inhaled anti-asthmatic drug showed no statistically significant association with cardiovascular defects, with odds ratio for the inhaled drug (OR=1.12)
Christensson et al., 2008 ⁹	Clinical review of scientific literature. Four studies using data from the Swedish birth and health registries	During pregnancy	Inhaled budesonide	No increased risk for congenital malformations, cardiovascular defects, decreased gestational age, birth weight or birth length among infants born to women using inhaled budesonide during pregnancy compared with the general population.

From applicant's submission dated May 30, 2018, PP-3 to 11, Table 2

⁸ Källén BA, Otterblad Olausson P. Maternal drug use in early pregnancy and infant cardiovascular defect. *Reprod Toxicol.* 2003 May-Jun;17(3):255-61

⁹ Christensson C, Thorén A, Lindberg B. Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. *Drug Saf.* 2008;31(11):965-88.

In a publication by Nicholl et al.,¹⁰ the authors report a case study of sixteen babies who received inhaled budesonide (100 mcg four times daily for 10 days via Aerochamber) or systemic steroids (dexamethasone 0.5 mg/kg/day, reducing over nine days). The gestational age, birth weight, and postnatal age were similar between the two groups. Inhaled budesonide had less short term effects on growth than systemically administered dexamethasone.

DPMH Review

No additional published information was identified since the 2016 DPMH consult review by Dr. Dinatale.

Pharmacovigilance Review

A search of the applicant's pharmacovigilance databases for comprehensive safety information from product development to present (i.e., March 24, 2010 to March 30, 2018) was performed. Three case reports with budesonide use in pregnancy were received. Two were identified in Switzerland from the published literature and one was received from the regulatory source in United Kingdom. Of the Swiss cases, one patient's infant was noted with congenital anomaly (nothing else is reported), while the other patient terminated the pregnancy following exposure in utero to budesonide and influenza vaccine (at 6th gestational week). No information was provided on budesonide dosing and exposure.

The other case was a regulatory case report from United Kingdom. A female infant, weight 2.23 kg, developed sepsis following in utero exposure to fluoxetine, budesonide, formoterol and salbutamol. The patient's mother started treatment with Formoterol (formoterol fumarate) BID, and Budesonide BID in [REDACTED] (b) (6) for the treatment of asthma. She was also under the treatment with Fluoxetine 10 mg for depression, and Salbutamol for asthma (dose not reported) during her pregnancy. On an unknown date, the baby developed sepsis and was transferred to a special care unit. It was reported that all the drugs were absorbed by baby via transplacental route. The outcome and causality for the event were not reported. No further information was provided.

Reviewer Comments:

The published experience (clinical trial, retrospective review of case series, epidemiological studies and review publications) with oral and inhaled budesonide do not show an increased risk of congenital malformations when budesonide is taken during pregnancy. Limitations of these studies include limited number of patients exposed to budesonide in some of them, retrospective nature and literature reviews with no meta analysis). Although the low dose inhaled budesonide (400mcg/day) does not appear to be associated with adverse effects in the fetus or neonate, different effects (like adrenal insufficiency/crisis, bone fracture, short stature) may be seen in offspring of women who use higher dose of oral budesonide. The systemic exposure from oral budesonide is greater than from inhaled budesonide, and the budesonide plasma concentration following a 9 mg daily dose of oral budesonide is up to ten times that of an 800 mcg daily dose of inhaled budesonide (see existing Entocort labeling).

In addition, current glucocorticoid labeling, including budesonide, states that

¹⁰ Nicholl RM, Greenough A, King M, Cheeseman P, Gamsu HR. Growth effects of systemic versus inhaled steroids in chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2002 Jul;87(1):F59-61

hypoadrenalism may occur in infants of mothers who have taken corticosteroid during pregnancy. This statement will be included in the “Clinical Considerations” section of Budesonide labeling.

Summary

There is evidence of embryofetal toxicity in animal reproduction studies performed with budesonide. The limited data identified on oral use of budesonide (most data is derived from inhaled budesonide for asthma treatment including some large population studies) during the use of budesonide in pregnancy cannot definitively establish the absence of risk during pregnancy. No major birth defects, miscarriage, or other adverse maternal or fetal outcomes have been identified with low and moderate doses of inhaled budesonide use during pregnancy; however, there are theoretical effects like adrenal insufficiency/crisis, bone fracture, short stature that may be seen in offspring of women who use oral budesonide during pregnancy. Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed for signs of hypoadrenalism (like fatigue, lethargy, muscle weakness, irritability, loss of appetite and weight loss).

LACTATION

Animal Data

No studies have been performed on budesonide use in lactating animals.

Review of Literature

Applicant’s Review

The applicant identified one study with use of inhaled budesonide during lactation. Fält et al.¹¹ collected milk and plasma samples up to 8 hours after dosing from 8 mothers receiving inhaled budesonide maintenance treatment (200 or 400 mcg twice daily) for asthma. Infant exposure was estimated based on average milk budesonide concentrations. Budesonide concentrations in milk reflected those in maternal plasma and were always lower than that in maternal plasma. The authors propose passive diffusion of budesonide between plasma and milk. The mean milk/plasma ratio was 0.46. The estimated daily infant dose was 0.3% of the daily maternal dose. The average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma. Budesonide concentrations in infant plasma samples were all less than the limit of quantification. The authors recommend continued use of inhaled budesonide during breastfeeding. There were no adverse events noted in the infants.

DPMH Review

No additional publications were identified in excess of those referenced in Dr. Dinatale’s review.

¹¹ Fält A, Bengtsson T, Kennedy BM, Gyllenberg A, Lindberg B, Thorsson L, Stråndgarden K. Exposure of infants to budesonide through breast milk of asthmatic mothers. *J Allergy Clin Immunol.* 2007 Oct;120(4):798-802.

Pharmacovigilance Review

The applicant did not identify any cases in their pharmacovigilance database.

Summary

Budesonide is present in human milk. One lactation study with inhaled budesonide demonstrated a milk/plasma ratio between 0.46 and a calculated daily infant dose of 0.3% of the daily maternal dose. There were no adverse events noted in the infants in the lactation study reported in literature. DPMH recommends that the Lactation section of Budesonide labeling should state the following:

“The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Budesonide and any potential adverse effects on the breastfed infant from Budesonide or from the underlying maternal condition.”

(b) (4)

Applicant’s and DPMH Review of literature

The applicant performed a search of published literature for available human fertility data for budesonide. DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of budesonide and its’ effects on fertility. No published data were found.

The applicant did not report any cases from the pharmacovigilance database.

Summary

There are no human data on the effects of budesonide on fertility and no evidence of infertility in animal studies. There are no recommendations for pregnancy testing nor contraception. Therefore, subsection 8.3, Females and Males of Reproductive Potential will not be included in Budesonide labeling.

CONCLUSIONS

Budesonide labeling has been revised to comply with the PLLR. A review of the literature for relevant data revealed no new data with budesonide use in pregnant or lactating women, and no data on budesonide effects on fertility. DPMH has the following recommendations for the Budesonide labeling:

- Pregnancy, Subsection 8.1
The “Pregnancy” subsection of Budesonide labeling was formatted in the PLLR format to include the “Risk Summary,” “Clinical Considerations,” and “Data” headings.
- Lactation, Subsection 8.2
The “Lactation” subsection of Budesonide labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” headings.

RECOMMENDATIONS

The below includes DPMH recommendations for the Budesonide labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling.

PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4) In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.5 times or 0.05 times, respectively, the maximum recommended human dose, resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels (*see Data*). Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

(b) (4)

(b) (4) Pregnant woman with Crohn's disease should be

(b) (4)

Fetal/Neonatal Adverse Reactions

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Infants should be carefully (b) (4) for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly [*see Warnings and Precautions (5.1)*].

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis from gestation days 6-15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6-18, increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses up to approximately 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis). Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.01 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis).

In a peri- and post-natal development study, rats dosed subcutaneously with budesonide during the period of Day 15 post coitum to Day 21 postpartum, budesonide had no effects on delivery but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures 0.02 times the MRHD (on a mg/m² basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity

8.2 Lactation

Risk Summary

Lactation studies have not been conducted with oral budesonide, including (b) (4) and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) and any potential adverse effects on the breastfed infant from (b) (4) or from the underlying maternal condition.

Data

One published study reports that budesonide is present in human milk following maternal inhalation of budesonide which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.4 and 0.5. Budesonide plasma concentrations were not detected and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide. The recommended daily dose of (b) (4) is higher (up to 9 mg daily) compared with inhaled budesonide (up to 800 mcg daily) given to mothers in the above described study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single- and repeated-dose pharmacokinetic studies) of oral budesonide is approximately 5-10 nmol/L which is up to 10 times higher than the 1-2 nmol/L for a 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of (b) (4) exposure to the breastfed infant may be up to 10 times higher than that by budesonide inhalation.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise female patients that [REDACTED] (b) (4) may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
12/19/2018

TAMARA N JOHNSON
12/19/2018

M E M O R A N D U M

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

DATE: December 07, 2018

TO: Dragos Roman, M.D.
Director (Acting)
Division of Gastroenterology & Inborn Errors Products
(DGIEP)
Office of Drug Evaluation III (ODEIII)
Office of New Drugs (OND)

Dale Conner, Pharm.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Li-Hong Yeh, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE
OSIS

SUBJECT: Routine inspection of Novum Pharmaceutical Research
Services, Houston, Texas.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of clinical studies 11742615 (NDA 211929) and ^{(b) (4)} conducted at Novum Pharmaceutical Research Services, Houston, Texas.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. However, the FDA Investigator observed that:

1. The certificate of analysis (COAs) of the reference listed drugs (RLD) used in studies 11742615 and ^{(b) (4)} were missing; and
2. The sponsor locked the database before the site's clinical investigator could follow the resolution of adverse events (AEs) in nine subjects in study 11742615.

Based on available inspectional evidence, I conclude that both findings do not impact the reliability of data from studies 11742615 and (b) (4). Despite the absence of COAs, the site's drug accountability records and forms completed by the FDA investigator indicate that the site dispensed the RLD specified in study reports submitted to FDA. Additionally, the site's "Clinical Comment Sheets" show that AEs from three of nine subjects resolved by day 30 following the last dose of study drug. The review division should assess the Clinical Comment Sheets of these three subjects (b) (6) in the safety evaluation of study 11742615 (**Exhibit 4**). The review division should also request AE resolution narratives listed as "unknown" for six subjects: (b) (6) (treatment B, mild); (b) (6) (treatment B, mild); (b) (6) (treatment A, mild); (b) (6) (treatment A, mild); (b) (6) (treatment B, mild), and (b) (6) (treatment B, mild) in study 11742615. The Establishment Inspection Report (EIR) does not mention whether the FDA investigator audited the six clinical comment sheets for these subjects. It is also unknown if the sheets are still available at the clinical site for Agency review. For additional details on the findings refer to section 3 below.

The final inspection classification for the inspected site is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the clinical data from the audited studies (Studies 11742615 and (b) (4)) are reliable for further Agency review. In addition, the clinical data from other studies of similar design conducted at Novum Pharmaceutical Research Services, Houston, Texas between the previous inspection (10/2017) and the end of the current surveillance interval should be reliable for review without an inspection.

2. Inspected Studies:

NDA 211929

Study Number: 11742615

Study Title: "A Study to Evaluate the Relative Bioavailability of a Test Formulation of Budesonide Capsules, 9 mg (Sun Pharmaceutical Industries Limited) Compared to an Equivalent Dose (3 x 3 mg) of ENTOCORT® EC (budesonide) Capsules, 3 mg (b) (4) in Healthy Adult Subjects under Fasted Conditions."

Dates of conduct: 08/16/2017 - 09/13/2017

Investigator Name: Robert A. Weaver, M.D.

(b) (4)

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(b) (4)

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2. Study 11742615 Protocol stated AEs should be followed up until they have resolved or stabilized or up to 30 days after study drug last dose. All AEs appeared to be verifiable in terms of being followed up and resolved per subjects' source document on "Clinical Comment Sheets", but the "Adverse Event Flowcharts" source documents appeared to document certain AEs with unknown outcomes, because the sponsor scheduled data lock (i.e., closure and release of all source charts and electronic case report forms [eCRFs] to data management) less than 30 days after study drug last dose. Three subjects (b) (6) cannot document resolution of their AE after (b) (6)

Site's response during the inspection: The site affirmed that all study charts and eCRFs were closed on 09/22/2017 for transmittal to Novum data management. Dr. Weaver closed out all outstanding AEs with pending resolution of 9 subjects reported to the FDA (Listing 16.2.7 Adverse Events) as Unknown (UNK) on (b) (6). Three subjects with AE follow-up were recorded in the Clinical Comment Sheet but this information were not reported to the FDA.

OSIS assessment: Nine subjects enrolled at Novum, Houston, Texas were reported to FDA with "unknown" AE resolution in study 11742615. Investigator Ngai was able to audit clinical comment sheets from three subjects (b) (6) (b) (6) that showed their AEs were resolved post database lock (**Exhibit 4**). However, the EIR does not mention if similar sheets were audited by FDA, or were available for audit for subjects (b) (6) (treatment B, mild); (b) (6) (treatment B, mild); (b) (6) (treatment A, mild); (b) (6) (treatment A, mild); (b) (6) (treatment B, mild), and (b) (6) (treatment B, mild). These subjects were also reported to FDA as having an "unknown" AE resolution.

The review division should assess the Clinical Comment Sheets of these three subjects in the safety evaluation of study 11742615 (**Exhibit 4**). The review division should also request AE resolution narratives listed as "unknown" for the remaining 6 subjects in study 11742615.

3. Conclusion:

After reviewing the inspectional findings, I conclude that the clinical data from studies 11742615 and (b) (4) are reliable for further Agency review. The lack of RLD COAs at the site for both studies did not impact data reliability.

The review division should review the resolution of AEs listed in clinical comment sheets collected for three subjects (b) (6) (b) (6) enrolled in study 11742615 (**Exhibit 4**). In addition, the review division should request from the sponsor AE resolution narratives for the remaining six subjects listed in the study report as "unknown" AE resolution. The EIR does not mention whether the FDA investigator audited the remaining six clinical comment sheets. It is also unknown if the sheets are still available at the clinical site for Agency review.

The clinical data from other studies of similar design conducted at Novum Pharmaceutical Research Services, Houston, Texas between the previous inspection (10/2017) and the end of the current surveillance interval should also be reliable for review without an inspection.

Li-Hong Yeh, Ph.D.
Chemist

Final Classification:

Clinical site

NAI - Novum Pharmaceutical Research Services

Houston, Texas
FEI#: 3003737189

cc:

OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Yeh
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: PY 12/03/2018; 12/06/2018; 12/07/2018
Edit: RCA 12/03/2018, 12/6/2018, 12/7/2018; AD 12/04/2018
12/06/2018

ECMS:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881a0ae16>

OSIS File #:

Direct

BE 8114 (NDA 211929)

(b) (4)

(b) (4)

FACTS: 11850279

Attachment 1
Studies in support of Pending Applications

Application #	Study #	Study Type (in vitro)	Drug Name	Dates of conduct
NDA 211929	11742615	In vivo	Budesonide	08/16/2017 - 09/13/2017

(b) (4)



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/s/

LI-HONG P YEH
12/07/2018

RUBEN C AYALA
12/07/2018

ARINDAM DASGUPTA
12/07/2018

M E M O R A N D U M

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

DATE: December 07, 2018

TO: Dragos Roman, M.D.
Director (Acting)
Division of Gastroenterology & Inborn Errors Products
(DGIEP)
Office of Drug Evaluation III (ODEIII)
Office of New Drugs (OND)

Dale Conner, Pharm.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Li-Hong Yeh, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE
OSIS

SUBJECT: Routine inspection of Novum Pharmaceutical Research
Services, Houston, Texas.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of clinical studies 11742615 (NDA 211929) and (b) (4) conducted at Novum Pharmaceutical Research Services, Houston, Texas.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. However, the FDA Investigator observed that:

1. The certificate of analysis (COAs) of the reference listed drugs (RLD) used in studies 11742615 and (b) (4) were missing; and
2. The sponsor locked the database before the site's clinical investigator could follow the resolution of adverse events (AEs) in nine subjects in study 11742615.

Based on available inspectional evidence, I conclude that both findings do not impact the reliability of data from studies 11742615 and (b) (4). Despite the absence of COAs, the site's drug accountability records and forms completed by the FDA investigator indicate that the site dispensed the RLD specified in study reports submitted to FDA. Additionally, the site's "Clinical Comment Sheets" show that AEs from three of nine subjects resolved by day 30 following the last dose of study drug. The review division should assess the Clinical Comment Sheets of these three subjects (b) (6) in the safety evaluation of study 11742615 (**Exhibit 4**). The FDA investigator confirmed that the AE for the remaining 6 subjects also resolved although no clinical comment sheets were available in the EIR. For additional details on the findings refer to section 3 below.

The final inspection classification for the inspected site is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the clinical data from the audited studies (Studies 11742615 and (b) (4)) are reliable for further Agency review. In addition, the clinical data from other studies of similar design conducted at Novum Pharmaceutical Research Services, Houston, Texas between the previous inspection (10/2017) and the end of the current surveillance interval should be reliable for review without an inspection.

2. Inspected Studies:

NDA 211929

Study Number: 11742615

Study Title: "A Study to Evaluate the Relative Bioavailability of a Test Formulation of Budesonide Capsules, 9 mg (Sun Pharmaceutical Industries Limited) Compared to an Equivalent Dose (3 x 3 mg) of ENTOCORT® EC (budesonide) Capsules, 3 mg (b) (4) in Healthy Adult Subjects under Fasted Conditions."

Dates of conduct: 08/16/2017 - 09/13/2017

Investigator Name: Robert A. Weaver, M.D.

(b) (4)

(b) (4)

2. Study 11742615 Protocol stated AEs should be followed up until they have resolved or stabilized or up to 30 days after study drug last dose. All AEs appeared to be verifiable in terms of being followed up and resolved per subjects' source document on "Clinical Comment Sheets", but the "Adverse Event Flowcharts" source documents appeared to document certain AEs with unknown outcomes, because the sponsor scheduled data lock (i.e., closure and release of all source charts and electronic case report forms [eCRFs] to data management) less than 30 days after study drug last dose. Three subjects (b) (6) cannot document resolution of their AE after (b) (6)

Site's response during the inspection: The site affirmed that all study charts and eCRFs were closed on 09/22/2017 for transmittal to Novum data management. Dr. Weaver closed out all outstanding AEs with pending resolution of 9 subjects reported to the FDA (Listing 16.2.7 Adverse Events) as Unknown (UNK) on (b) (6). Three subjects with AE follow-up were recorded in the Clinical Comment Sheet but this information were not reported to the FDA.

OSIS assessment: Nine subjects enrolled at Novum, Houston, Texas were reported to FDA with "unknown" AE resolution in study 11742615. Investigator Ngai was able to audit clinical comment sheets from three subjects (b) (6) (b) (6) that showed their AEs were resolved post

database lock (**Exhibit 4**). ORA verified that AEs from remaining 6 subjects also resolved (**Exhibit 5**).

The review division should assess the Clinical Comment Sheets of these three subjects in the safety evaluation of study 11742615 (**Exhibit 4**).

3. Conclusion:

After reviewing the inspectional findings, I conclude that the clinical data from studies 11742615 and (b) (4) are reliable for further Agency review. The lack of RLD COAs at the site for both studies did not impact data reliability.

The review division should review the resolution of AEs listed in clinical comment sheets collected for three subjects (b) (6) (b) (6) and (b) (6) enrolled in study 11742615 (**Exhibit 4**). The FDA investigator confirmed that the AE for the remaining 6 subjects also resolved although no clinical comment sheets were available in the EIR.

The clinical data from other studies of similar design conducted at Novum Pharmaceutical Research Services, Houston, Texas between the previous inspection (10/2017) and the end of the current surveillance interval should also be reliable for review without an inspection.

Li-Hong Yeh, Ph.D.
Chemist

Final Classification:

Clinical site

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Houston, Texas
FEI#: 3003737189

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OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: PY 12/03/2018; 12/06/2018; 12/07/2018
Edit: RCA 12/03/2018, 12/6/2018, 12/7/2018; AD 12/04/2018
12/06/2018

ECMS:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881a0ae16>

OSIS File #:

Direct

BE 8114 (NDA 211929)

(b) (4)

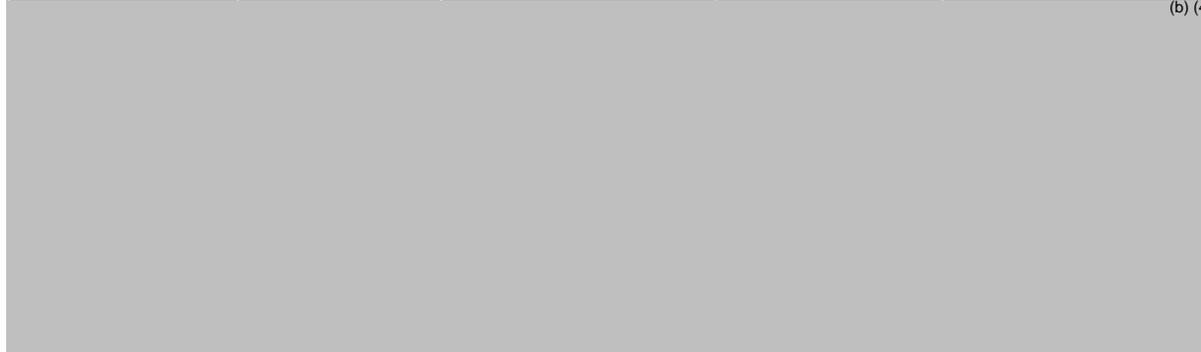
(b) (4)

FACTS: 11850279

Attachment 1
Studies in support of Pending Applications

Application #	Study #	Study Type (in vitro)	Drug Name	Dates of conduct
NDA 211929	11742615	In vivo	Budesonide	08/16/2017 - 09/13/2017

(b) (4)



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/s/

LI-HONG P YEH
12/07/2018

RUBEN C AYALA
12/07/2018

ARINDAM DASGUPTA
12/07/2018

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:	October 19, 2018
Requesting Office or Division:	Division of Gastrointestinal and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 211929
Product Name and Strength:	budesonide capsule, 6 mg and 9 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sun Pharma Global FZE
Submission Dates:	March 30, 2018 June 25, 2018
OSE RCM #:	2018-669
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 REASON FOR REVIEW

This review evaluates the labels and labeling for budesonide (NDA 211929), 505 b(2) NDA, submitted on March 30, 2018. On June 25, 2018, revised prescribing information (PI) was submitted. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed PI and container labels for any 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.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Sun Pharma Global FZE submitted a 505 b(2) NDA for budesonide capsules for treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older and maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults. The reference listed drug (RLD) for this NDA is Entocort EC 3 mg oral capsules. Sun Pharma has developed the higher strength capsules to reduce the number of capsules to be taken daily. The active ingredient, proposed indication, dosage form, dose, route of administration and duration of administration of the proposed product will be the same as the RLD.

We identified areas in the PI and container labels that can be improved to increase the clarity of information to promote the safe use of the product. We defer to DGIEP and Office of Pharmaceutical Quality (OPQ) for the appropriateness of the dosage form and (b) (4)

(b) (4) We provide letter-ready recommendations for the Applicant in Section 4.1 to address our concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and container labels can be improved to increase the clarity of information to promote the safe use of the product. We provide our recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR SUN PHARMA GLOBAL FZE

We recommend the following be implemented prior to approval of this NDA:

A. Container labels:

1. Once a proprietary name is found acceptable, ensure that the container labels are updated and submitted for review.
2. As currently displayed, lot number statement is missing. As per 21 CFR 201.10(i)(1), lot number is required on the container label when there is sufficient space.
3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either
DDMMYYYY (e.g., 31JAN2013)
MMYYYY (e.g., JAN2013)
YYYY-MMM-DD (e.g., 2013-JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for budesonide that Sun Pharma submitted on March 30, 2018 and June 25, 2018.

Table 2. Relevant Product Information for budesonide		RLD Entocort EC
Initial Approval Date	N/A	October 2, 2001
Active Ingredient	budesonide	
Indication	Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older. Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults.	
Route of Administration	oral	
Dosage Form	capsule	
Strength	6 mg and 9 mg	3 mg
Dose and Frequency	Mild to moderate active Crohn's disease: Adults: 9 mg once daily for up to 8 weeks; repeat 8 week treatment courses recurring episodes of active disease. Pediatrics 8 to 17 years who weigh more than 25 kg: 9 mg once daily for up to 8 weeks, followed by 6 mg once daily in the morning for 2 weeks. Maintenance of clinical remission of mild to moderate Crohn's disease: Adults: 6 mg once daily for up to 3 months; taper to complete cessation after 3 months. Continued treatment for more than 3 months has not been shown to provide substantial clinical benefit. When switching from oral prednisolone, begin tapering prednisolone concomitantly with initiating budesonide capsules.	
How Supplied	Bottles of 30s, 100s and 500s.	bottles of 100
Storage	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the budesonide labels and labeling submitted by Sun Pharma on March 30, 2018 and June 25, 2018.

- Container labels
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SHERLY ABRAHAM
10/19/2018

SARAH K VEE
10/23/2018