

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202129Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: December 19, 2011

To: Colette Jackson, Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matthew Falter, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP), Office of
Prescription Drug Promotion (OPDP)
Roberta Szydlo, Regulatory Review Officer
Division of Professional Promotion (DPP), OPDP

CC: Lisa Hubbard, Group Leader, DPP
Robyn Tyler, Group Leader, DDTCP
Olga Salis, Project Manager, OPDP

Subject: NDA 202129
OPDP labeling comments for Ciclesonide Nasal Aerosol

OPDP has reviewed the proposed Package Insert (PI), proposed Patient Package Insert (PPI), proposed Instructions for Use (IFU), and Carton and Container Labeling for Ciclesonide Nasal Aerosol submitted for consult on May 17, 2011, and offers the following comments.

OPDP's comments on the PI, PPI, and IFU are based on the proposed draft marked-up labeling titled "120811_Proposed_FDAeditsV8.doc" that was sent via e-mail from DPARP to OPDP on December 8, 2011. OPDP's comments on the PI, PPI, and IFU are provided directly in the marked-up document attached (see below).

OPDP's comments on the proposed carton and container labeling are based on the draft labeling submitted by the sponsor on December 15, 2011, and located in the EDR at:

- <\\cdsesub1\EVSPROD\NDA202129\0000\m1\us\114-label\1141-draft-label\11411-draft-carton-contain\sample-canister-label-30-act.pdf>

- <\\cdsesub1\EVSPROD\NDA202129\0000\m1\us\114-label\1141-draft-label\11411-draft-carton-contain\sample-carton-30-act.pdf>
- <\\cdsesub1\EVSPROD\NDA202129\0000\m1\us\114-label\1141-draft-label\11411-draft-carton-contain\sample-actuator-label-30-act.pdf>
- <\\cdsesub1\EVSPROD\NDA202129\0000\m1\us\114-label\1141-draft-label\11411-draft-carton-contain\trade-canister-60-act.pdf>
- <\\cdsesub1\EVSPROD\NDA202129\0000\m1\us\114-label\1141-draft-label\11411-draft-carton-contain\trade-carton-60-act.pdf>
- <\\cdsesub1\EVSPROD\NDA202129\0000\m1\us\114-label\1141-draft-label\11411-draft-carton-contain\trade-actuator-60-act.pdf>

We offer the following comments on the proposed Carton and Container labeling:

General:

We recommend that the established name be revised on the carton and container labels to a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

Carton:

We note that the carton labeling states, [REDACTED] (b) (4)

[REDACTED] We are concerned that this statement may be misleading if presented in the context of promotional material [REDACTED] (b) (4)

[REDACTED] If this statement is not considered essential, we suggest that it be deleted.

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

If you have any questions regarding the PI or the Carton and Container Labeling, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

If you have any questions regarding the PPI or the IFU, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

24 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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/s/

ROBERTA T SZYDLO
12/19/2011

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

PATIENT LABELING REVIEW

Date: **December 16, 2011**

To: **Badrul Chowdhury, MD, Director
Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)**

Through: **LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)**

**Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs**

From: **Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs**

Subject: **DMPP Review of Patient Labeling (Patient Package Insert
and Instructions for Use)**

Drug Name (established name): **(ciclesonide)**

Dosage Form and Route: **Nasal Aerosol**

Application Type/Number: **202129**

Applicant: **Sunovion Pharmaceuticals Inc.**

OSE RCM #: **2011-1200**

1 INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for ciclesonide nasal aerosol.

On March 18, 2011, Nycomed submitted a new drug application for ciclesonide nasal aerosol for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. Nycomed has authorized Sunovion Pharmaceuticals Inc. to act as US Agent for NDA 202129. A TRADENAME has not yet been designated for ciclesonide nasal aerosol. Therefore, we have used TRADENAME throughout the DMPP review of the Patient Package Insert and Instructions for Use.

2 MATERIAL REVIEWED

- Draft ciclesonide Patient Package Insert (PPI) received on March 21, 2011 and received by DMPP on December 9, 2011
- Draft ciclesonide Instructions for Use (IFU) received on March 21, 2011 and received by DMPP on December 9, 2011
- Draft ciclesonide Prescribing Information (PI) received on March 21 2011, revised by the Review Division throughout the current review cycle and received by DMPP on December 9, 2011

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 have reformatted the PPI document using the Verdana font, size 11.

In our 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI and IFU are appended to this memo. Consult DMPP 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.

27 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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/s/

SHARON W WILLIAMS
12/16/2011

MELISSA I HULETT
12/16/2011

LASHAWN M GRIFFITHS
12/19/2011

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Transplant and Ophthalmology Products**

FROM (Name, Office/Division, and Phone Number of Requestor):

Colette Jackson, Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

DATE December 14, 2011	IND NO.	NDA NO. 202129	TYPE OF DOCUMENT N	DATE OF DOCUMENT December 9, 2011
NAME OF DRUG Ciclesonide Nasal Aerosol		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Pro-corticosteroid	DESIRED COMPLETION DATE January 4, 2012

NAME OF FIRM: **Nycomed c/o Sunovion (US Agent)**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: We are evaluating NDA 202129 for an HFA formulation of ciclesonide, a nasal steroid proposed for the treatment of seasonal and perennial allergic rhinitis. For this application, the sponsor did not conduct specific ocular safety studies, but made reference to studies from the Omnaris program (NDA 22004), an aqueous formulation of the same active moiety. However, the systemic and local exposure to the HFA product is greater than Omnaris. Also, two nasal septal perforations were observed in 2 week pivotal trials with the HFA formulation, raising concerns of local safety. As such, we are requiring a post-marketing safety study to assess for local toxicity, including ocular findings. The sponsor has submitted a study synopsis for the required study. This submission is located in the EDR: \\CDSESUB1\EVSPROD\NDA202129\202129.enx. eCTD sequence 0025.

Please provide comments on the adequacy of the proposed ocular assessments in the safety trial.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

COLETTE C JACKSON
12/14/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: December 9, 2011

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name/Strength: Ciclesonide Nasal Aerosol
37 mcg per actuation

Application Type/Number: NDA 202129

Applicant/sponsor: Sunovion Pharmaceuticals Inc.

OSE RCM #: 2011-1199

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

1 INTRODUCTION

The review responds to a request from the Division of Pulmonary Allergy and Rheumatology Products (DPARP) to review the container labels and carton labeling of Ciclesonide Nasal Aerosol (NDA 202129) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

Ciclesonide is currently marketed under the proprietary names Omnaris (NDA 022004) approved in October 2006 and Alvesco (NDA 021658) approved January 2008.

Omnaris is a nasal spray indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children six years of age and older and perennial allergic rhinitis in adults and adolescents 12 years of age and older. It is supplied in a 12.5 gram bottle that delivers 120 metered actuations of 50 mcg per actuation. The usual dosage is two sprays per nostril once daily.

Alvesco is an aerosol for oral inhalation indicated for the maintenance treatment of asthma as prophylactic therapy in adults and adolescent patients 12 years of age and older. It is supplied in a 6.1 gram canister that delivers 60 metered actuations of either 80 mcg or 160 mcg per actuation. The usual dosage is one to two inhalations by mouth twice daily.

The current application under review is for a nasal aerosol indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. It will be supplied in a 6.1 gram canister that delivers 60 metered actuations of 37 mcg per actuation. The usual dose is one inhalation per nostril once daily.

1.2 PRODUCT INFORMATION

The following product information is provided in the October 21, 2011 proprietary name submission.

- Established Name: Ciclesonide
- Indication of Use: Treatment of Symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older
- Route of administration: Nasal
- Dosage form: Nasal Aerosol
- Dose: 74 mcg per day given as one actuation per nostril once daily
- How Supplied: 6.1 gram canister for a 30 day supply (60 actuations) and a professional sample canister containing 4.7 grams for a 15 day supply (30 actuations)
- Storage: 25°C (77°F) excursions between 59-86°F are permitted
- Container and Closure systems: a canister inserted into a purple/white nasal actuator with a purple dust cap

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 19, 2011
- Carton Labeling submitted March 19, 2011
- Prescribing Information and Instructions for Use submitted June 23, 2011

Additionally, since Ciclesonide is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Ciclesonide. The October 24, 2011 AERS search used the following search terms: trade name “Ciclesonide”, and verbatim terms “Ciclesoni%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. No time limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error (i.e. intentional overdose), adverse drug reaction, patient non-adherence, and medication errors not related to this product.

Following exclusions there were no cases relevant to this review.

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling may introduce vulnerability that can lead to medication errors. We recommend the following:

A. General Comments (All Container Labels and Carton Labeling)

1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast and other printing features as stated in 21 CFR 201.10 (g)(2).
2. Increase the prominence of the strength statement (i.e. 37 mcg per actuation).
3. Relocate and decrease the prominence of the statement that reads “60 metered actuations” on the trade container labels and carton labeling and “30 metered actuations” on the professional sample label and carton labeling to the bottom of the container label and carton labeling, away from the strength statement. As currently presented it is more prominent than more relevant information such as the established name and the strength.

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

4. Revise the route of administration statement to read “For Intranasal Use Only” on a single line. To achieve this you should present the statements “Use with Trade Name Nasal Aerosol Actuator Only” or “Use with Trade name Nasal Aerosol Canister Only” on the line immediately below the route of administration statement as shown below.

For Intranasal Use Only

Use with Trade Name Nasal Aerosol Actuator Only

Or

For Intranasal Use Only

Use with Trade Name Nasal Aerosol Canister Only

B. All Carton Labeling (Trade and Professional Sample)

Revise the statement [REDACTED] (b) (4)
[REDACTED] to read “Usual Dosage: See Prescribing Information”

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

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/s/

CARLOS M MENA-GRILLASCA on behalf of LISSA C OWENS
12/09/2011

CARLOS M MENA-GRILLASCA
12/09/2011

CAROL A HOLQUIST
12/12/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 202129

Name of Drug: Ciclesonide Nasal Aerosol

Applicant: Nycomed c/o Sunovion

Material Reviewed:

Submission Date(s): March 18, 2011

Receipt Date(s): March 21, 2011

Submission Date of Structure Product Labeling (SPL): March 18, 2011

Type of Labeling Reviewed: WORD

Background and Summary

On March 18, 2011, Nycomed submitted a New Drug Application for Ciclesonide Nasal Aerosol for the treatment of seasonal and perennial allergic rhinitis in patients 12 years of age and older.

The proposed labeling text for Ciclesonide Nasal Aerosol was provided in SPL. Draft labeling text was provided in WORD (.doc) format as a review aid, submitted by Nycomed also on March 18, 2011.

Review

Primary reviewer: Colette Jackson, Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
OND, ODE II, CDER

The .xml version of the proposed labeling in the new PLR format was reviewed using the Label Review Tool provided by SEALD. The following are comments and recommendations for the proposed labeling that should be conveyed to the applicant in the 74-day letter

Recommendations

Please address the identified deficiency/issue and re-submit the labeling. This updated version of labeling will be used for further labeling discussions.

The following comment pertains to the Highlights Overview section of the product label.

1. There should be a white space between each major heading in the Highlights.

The following comment pertains to the Table of Contents section of the product label.

2. The section headings must be in bold type and should be in upper case letters.

The following comment pertains to the Table of Contents and Full Prescribing Information sections of the product label.

3. There should be no periods after the numbers for the section and subsection headings.

The following comment pertains to the Highlights Overview and Full Prescribing Information sections of the product label.

4. Do not use a slash mark (/) since it may be mistaken for the number 1. Use “per”. For example, do not use 12 mg/kg. Use 12 mg per kg.

Colette Jackson
Regulatory Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: CCJ/ May 26, 2011

Revised/Initialed: Barnes/ June 2, 2011
Finalized: CCJ/ June 15, 2011
Filename: 202129 PLR Labeling Review
CSO LABELING REVIEW OF PLR FORMAT

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/s/

COLETTE C JACKSON
06/15/2011

SANDRA L BARNES
07/15/2011

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 # 202129 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: ciclesonide Dosage Form: nasal aerosol Strengths: 37 mcg		
Applicant: Nycomed Agent for Applicant (if applicable): Sunovion		
Date of Application: March 18, 2011 Date of Receipt: March 21, 2011 Date clock started after UN:		
PDUFA Goal Date: January 21, 2012	Action Goal Date (if different): January 20, 2012	
Filing Date: May 20, 2011 (actual 5/21/2011)	Date of Filing Meeting: May 2, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): SAR and PAR in patients 12 years of age and older		
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" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <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>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input checked="" type="checkbox"/> N/A	Resubmission after refuse to file? <input checked="" type="checkbox"/> N/A	
Part 3 Combination Product? <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <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): 74,674; 53,391; 65,488				
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>	X			
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>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
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>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><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></p>	<p>Payment for this application:</p> <p><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</p>																			
<p><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></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>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)].</p>																				
<p>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)]?</p> <p><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 (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below: (see attached)</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><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 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</p>		<p>X</p>																		

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

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<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)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>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:</p>	X			

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?				
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)?	X			
<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?		X		Reference is made to section 3.2.P.3.1
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<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?	X			
<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?	X			

<p><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></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic

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

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><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 reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

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

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
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>	X			
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>		X		
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>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input 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 checked="" type="checkbox"/> Other (specify) Patient Information			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

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

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<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? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): December 15, 2008, and CMC January 9, 2008 <i>If yes, distribute minutes before filing meeting</i>	X			CMC meeting was cancelled due to sponsor receipt of meeting comments

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): November 3, and December 21, 2010 (CMC) <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 2, 2011

NDA: 202129

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: ciclesonide

DOSAGE FORM/STRENGTH: nasal aerosol/37 mcg

APPLICANT: Nycomed c/o Sunovion

PROPOSED INDICATION(S): SAR and PAR in patients 12 years of age and older

BACKGROUND: This is a new dosage form of ciclesonide. ALVESCO® Inhalation Aerosol and OMNARIS® Nasal Spray, which are also sponsored by Nycomed GmbH, are the only drug products that have been approved under Section 505(b) of the Act that contain any active moiety of the drug for which the applicant is seeking approval.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Colette Jackson	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Theresa Michele		Y
Clinical	Reviewer:	Robert Lim	Y
	TL:	Theresa Michele	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ying Fan	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Robert Abugov for Qian Li	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Y
	TL:	Molly Topper for Timothy Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Art Shaw	Y
	TL:	Alan Schroeder	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	Y
	TL:	Todd Bridges	N
OSE/DRISK	Reviewer:	Sharon Williams	N
	TL:	Melissa Hulett	N
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Nichelle Rashid, OSE RPM		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <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: none</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" 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:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <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</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>or efficacy issues</i></p> <ul style="list-style-type: none"> ○ <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:</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:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</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>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" 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:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</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:</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 style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <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 DMPQ? <p>Comments:</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

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul A. Chowdhury, M.D., Ph.D.	
21st Century Review Milestones : Filing/Planning Meeting: May 2, 2011 Filing Reviews Due: May 5, 2011 60th Day Letter Due: May 20, 2011 (request to sign off by May 19 th) 74-Day Letter Due: June 3, 2011 Team Meeting: July 5, 2011 Mid-Cycle Meeting: August 12, 2011 Labeling Meeting: November 30, 2011 PeRC: November 30, 2011 Wrap-Up: December 6, 2011 Label due to the Company: December 13, 2011 Labeling Tcon/PMR/PMC discussion with Applicant: December 20, 2011 Primary Reviews: December 16, 2011 Secondary Reviews: December 23, 2011 CDTL Memo Due: December 30, 2011	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input 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"/>	If priority review: <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 DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

COLETTE C JACKSON
06/15/2011

DSI CONSULT: Request for Clinical Inspections

Date: May 25, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Joseph Salewski, Branch Chief (Acting), GCP2
Tejashri Purohith-Sheth, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Robert Lim, MD, Medical Officer, through
Theresa M. Michele MD, Medical Team Leader, through
Badrul Chowdhury, MD, PhD, Division Director
Division of Pulmonary, Allergy, and Rheumatology Products

From: Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-202129

Sponsor/Sponsor contact information (to include phone/email):

Renee M. Carroll, MS, RAC
Senior Director, Regulatory Affairs
Sunovion Pharmaceuticals, Inc.
(tel) 508-357-7598
(fax) 508-357-7491
(e-mail) renee.carroll@sunovion.com

Drug: Trade Name (generic): ciclesonide HFA nasal aerosol

NME (Yes/No): No

Review Priority (Standard or Priority): Standard

Study Population includes < 18 years of age (Yes/No): Yes (down to 12 years)

Is this for Pediatric Exclusivity (Yes/No): No

PDUFA: January 21, 2012
Action Goal Date: January 20, 2012
Inspection Summary Goal Date: August 10, 2011

II. Background Information

New Application or Supplement? New Application

Indication: “for treatment of symptoms associated with seasonal and perennial allergic rhinitis (PAR and SAR) in adults and adolescents 12 years of age and older”

Drug: Ciclesonide is a non-halogenated glucocorticoid that is rapidly metabolized to des-ciclesonide. This metabolite has a very high affinity for the glucocorticoid receptor, and is primarily responsible for this drug’s pharmacologic activity. The sponsor developed this product to meet the needs of patients who prefer an HFA delivery system over an aqueous nasal spray. An aqueous suspension of ciclesonide is currently approved for use in patients with SAR/PAR as a nasal spray in patients 6 years old and older (Omnaris, NDA 22,004). In addition, ciclesonide is also approved to be delivered via an HFA MDI for chronic therapy in asthma in patients 12 years and older (Alvesco, NDA 21,658).

Disease: Allergic rhinitis (AR) is a common allergic condition, defined as a symptomatic disorder of the nose induced by immunoglobulin-E (IgE)-mediated inflammation after allergen exposure to the mucous membranes of the nose. Symptoms of AR include rhinorrhea, nasal obstruction, nasal itching and sneezing, but can be accompanied by eye symptoms. AR has traditionally been classified as SAR or PAR, depending on whether an individual is sensitized to seasonal pollens or year round allergens. The pathophysiology of SAR and PAR are comparable, other than for the inciting allergen and chronicity of symptoms

III. Protocol/Site Identification

Nycomed/Sunovion submitted a new NDA for ciclesonide HFA nasal aerosol for treatment of symptoms associated with PAR and SAR in adults and adolescents 12 years and older. To support the efficacy and dosing claims, Nycomed/Sunovion submitted results from 4 clinical trials. Trial M1-602 was a dose ranging study in patients with SAR conducted at 35 sites in the U.S. Trial 060-633 was an efficacy/safety study in patients with PAR conducted at 46 U.S. sites. Trials 060-622 and 060-634 were efficacy/safety studies in patients with SAR and conducted at 8 sites in Texas. For all trials, ear nose throat exams were periodically performed to assess for local reactions. Two nasal septal perforations in patients on test article were noted in this development program. In general, it is rare for perforations to occur in a nasal steroid development program, and their occurrence is of particular concern.

M1-602: This was double-blind, randomized, placebo controlled, dose ranging study in which SAR patients were given either placebo, 80 mcg, 160 mcg, or 320 mcg daily of the test product for 2 weeks. The study consisted of a run in period and a treatment period. During the run-in period, all patients received placebo and assessed/recorded their instantaneous and reflective nasal and non-nasal symptoms. Following the run-in period, patients were randomized to one of the three doses and followed for 14 days. During this period they continued to assess their nasal and non-nasal

symptoms. A total of 513 patients were randomized. During this trial one patient receiving the 80 mcg dose developed a nasal septal perforation.

Trial 060-622: This was double-blind, randomized, placebo controlled, parallel group, multi-center study in SAR patients given either placebo, 80 mcg or 160 mcg daily of the test product for 2 weeks. The study consisted of a screening period, followed by a 7 day single blind placebo run in period, a 14 day treatment period, and a wash-out period. Nasal and non-nasal symptoms were assessed during all periods except the wash-out period. A total 707 patients were randomized.

Trial 060-634: This study was almost identical in design to study 060-622. A total of 671 patients were randomized. One patient receiving the 80mcg dose developed a nasal septal perforation.

Trial 060-633: This was a 6 month multi-center, randomized, double-blind placebo controlled, parallel group efficacy and safety study of ciclesonide in patients 12 years and older with PAR. Patients were given either placebo, 80 mcg or 160 mcg daily following randomization. This study consisted of a screening period, followed by a single blind run in period. The double blind treatment period followed the run-in period and lasted 26 weeks Symptoms were assessed as in the previously mentioned studies. A total of 1111 patients were randomized. At the end of this study, patients were allowed to continue in a 6 month open label safety extension (060-635).

IV. Site Selection/Rationale

We are requesting audits of 2 domestic sites for this application from trials M1-602, 060-622, 633, and 634. For this purpose, we have submitted 4 sites for your consideration.

The sites were reviewed for audit selection based on the following criteria: 1) occurrence of nasal septal perforation, 2) enrollment, 3) adverse events (AEs), and 4) previous audit (Nycomed/Sunovion or FDA). Based on these criteria, 4 potential sites were selected for audit and are listed below in order of preference.

Robert Lee Jacobs, MD (site 003 in trials 060-622/634 and site 14 in trial 060-633)
Biogenics Research Institute
8233 Fredericksburg Road
San Antonio, TX 78229
210-614-2564

Although the above listed site was audited by the sponsor, 1 of the 2 septal perforations reported in this development program occurred at this site. In addition, in trials 060-622/634, this site randomized the most patients (224 patients total), and was also in the top quartile in terms of randomized patients in study 060-633 (39 patients). The septal perforation occurred in study 060-634.

Pinkus Goldberg, MD (site 10 in trial 060-633, also a site in M1-602)
Clinical Research Center of Indiana
3266 N. Meridian St. Suite 900
Indianapolis, IN 46208

This site listed above was also audited by the sponsor; however, during trial M1-602, a septal perforation was noted. This site also participated in 060-633 and was in the top quartile in terms of randomized patients (30) and adverse events (total and nasal related).

Frank Hampel Jr., MD (site 2 in trials 060-622/060-634 and site 12 in trial 060-633)
Central Texas Health Research
705-A Landa Street
New Braunfels, TX 78130
830-629-9036

This above site randomized the 3rd most patients overall in studies 060-622 and 060-634 (194 patients total), and had the highest number of AEs. This site also randomized an average number of patients in study 060-633 (23 patients). This site was also not previously audited.

Stephen A. Tilles, MD (site 0042 in trial 060-633)
ASTHMA, Inc.
4540 Sand Point Way NE, Suite 100
Seattle, WA 98105
206-527-1200

This site had the highest number of AEs (total and nasal), was not previously audited, and recruited an average number of patients for study 060-633 (25 patients).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): nasal septal perforations, other AEs. In addition to normal audit parameters, please evaluate adequacy of medication use instructions, as improper use may increase risk of septal perforations.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify):

Five or More Inspection Sites: N/A

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

V. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Colette Jackson at Ph: 301-796-1230 or Robert Lim, MD at Ph: 301-796-1236.

Concurrence: (as needed)

Robert Lim, MD, Medical Officer
Theresa Michele, MD, Medical Team Leader
Badrul Chowdhury, MD, PhD Director, Division Director (for foreign inspection requests only)

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/s/

COLETTE C JACKSON
05/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: CDER-DDMAC-RPM		FROM: Colette Jackson Senior Regulatory Health Project Manager Division of Pulmonary, Allergy, and Rheumatology Products	
REQUEST DATE May 17, 2011	IND NO.	NDA/BLA NO. 202129	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Ciclesonide Nasal Aerosol	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Corticosteroid	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) November 29, 2011
NAME OF FIRM: Nycomed		PDUFA Date: January 21, 2012	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
		REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
EDR link to submission: The labeling is electronic and can be found at \\CDSESUB1\EVSPROD\NDA202129\202129.enx .			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.			
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: August 12, 2011 Labeling Meetings: November 30, and December 20, 2011 Wrap-Up Meeting: December 6, 2011			
SIGNATURE OF REQUESTER			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

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COLETTE C JACKSON
05/17/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): OSE		FROM: Colette Jackson Senior Regulatory Health Project Manager Division of Pulmonary, Allergy, and Rheumatology Products		
DATE March 31, 2011	IND NO.	NDA NO. 202129	TYPE OF DOCUMENT N	DATE OF DOCUMENT March 18, 2011
NAME OF DRUG Ciclesonide Nasal Aerosol		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Corticosteroid	DESIRED COMPLETION DATE November 30, 2010
NAME OF FIRM: Nycomed				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: This is a request for a consult on the carton and container labeling for NDA 202129 The labeling is electronic and can be found at \\CDSESUB1\EVSPROD\NDA202129\202129.enx . PDUFA DATE: January 21, 2012 ATTACHMENTS: CC: Archival NDA 202129 HFD-570/Division File HFD-570/Jackson				
SIGNATURE OF REQUESTER Colette Jackson 6-1230		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

COLETTE C JACKSON
03/31/2011